

EXHIBIT 18

AUROBINDO'S MOTION *IN LIMINE* NO. 1

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AMICUS THERAPEUTICS US, LLC
and AMICUS THERAPEUTICS, INC.,

Plaintiffs,

v.

TEVA PHARMACEUTICALS USA, INC.,
and TEVA PHARMACEUTICALS, INC., *et al.*

Defendants.

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: C.A. No. 1:22-cv-01461-CJB
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: ANDA Case
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: (Consolidated)
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EXHIBIT 18

AUROBINDO'S MOTION *IN LIMINE* NO. 1:
PRECLUSION/EXCLUSION OF PLAINTIFFS'
EXPERT TESTIMONY REGARDING THE HEK ASSAY

Plaintiffs' experts, Drs. Robert J. Hopkin and John L. Jeffries, agree with Aurobindo on at least one point: Neither Dr. Hopkin nor Dr. Jeffries is the leastwise qualified to offer testimony regarding the laboratory diagnostic tool that features prominently in this case, the so-called HEK Assay. Aurobindo respectfully submits they should, therefore, be precluded from doing so in accordance with Federal Rule of Evidence 702.

As issue in this Motion is the HEK Assay, a laboratory-run diagnostic tool that can be used to determine whether a Fabry Disease patient's genetic mutation renders the patient amenable to treatment with migalastat, the active pharmaceutical ingredient in the drug products at issue in this case. Notably, there is no dispute that the HEK Assay itself is not claimed or described in the Asserted Claims. The Asserted Claims are not directed to running the HEK Assay or identifying or selecting Migalastat-amenable patients. They are simply directed to methods of treating certain Fabry Disease patients with migalastat. Plaintiffs nonetheless point to their latest iteration of the HEK Assay, the so-called GLP-HEK Assay, as somehow negating the invalidity of the Asserted Claims, and the unsworn written expert reports Plaintiff produced from Drs. Hopkin and Jeffries include opinions regarding the HEK Assay, which neither of them has ever used or can even explain in any detail. Thus, Plaintiffs' expert strategy, much like their strategy for distracting the Court with fictitious movies *inter alia*, is grounded in impermissible obfuscation. Aurobindo respectfully requests that Plaintiffs not be permitted to tie up precious trial time with opinions from experts who have openly admitted under oath they are not qualified to offer.

To testify at trial, experts must be "qualified" to do so by "knowledge, skill, experience, training or education." *See* Fed. R. Evid. 702; *see also Withrow v. Spears*, 967 F. Supp. 2d 982, at 991-95 (D. Del. 2013) (Burke, M.J.) (excluding expert testimony due to lack of qualifications); *Eaton Corp. v. Rockwell Int'l Corp.*, C.A. No. 97-421, 2001 U.S. Dist. LEXIS 17054, *62-*64 (D.

Del. Oct. 10, 2001) (Farnan, D.J.) (excluding expert testimony based on admitted lack of qualifications). In determining whether Rule 702 permits expert testimony, the Court must assess (a) “whether the expert witness has specialized knowledge regarding the area of testimony,” (b) whether the proffered testimony is “supported by appropriate validation,” and (c) whether the proffered testimony would (i) “assist the trier of fact to understand the evidence or to determine a fact in issue and [(2)] have a valid scientific connection to the pertinent inquiry as a precondition to admissibility.” *Withrow*, 967 F. Supp. 2d at 991-92 (internal quotations omitted). “Overall, Rule 702 embodies a liberal policy of admissibility. Nonetheless, the burden is placed on the party offering expert testimony to show that it meets each of the standards for admissibility.” *Id.* at 992 (internal quotations and citations omitted). Aurobindo respectfully submits Plaintiffs cannot meet any of these requirements with respect to the HEK Assay.

At their depositions, under oath, Dr. Hopkin and Dr. Jeffries clearly, repeatedly, and unequivocally denied having knowledge of the HEK Assay such that their testimony on the subject could be considered reliable or valid to any degree. (*See* Hopkin (non-final) Dep. Tr. at 67:21-68:21, 70:4-17, 71:10-72:19, 77:3-10, 113:1-7, 168:24-169:8, 195:5-196:16 (**Exhibit A** hereto); Jeffries Dep. Tr. at 98:25-100:4, 101:4-20; 102:20-104:10 (**Exhibit B** hereto).) By their own sworn admissions, neither Dr. Hopkin nor Dr. Jeffries has ever run a HEK Assay, knows how to run a HEK Assay or is familiar with the details of any HEK Assay, let alone familiar enough to draw comparisons and distinctions between various iterations of HEK Assays. Therefore, they should not be permitted to offer testimony regarding the HEK Assay. *See Withrow*, 967 F. Supp. 2d at 994-95 (noting as a basis for excluding testimony the expert’s own deposition disclaimer of knowledge and qualifications).

To be clear, Aurobindo is not seeking to preclude Plaintiffs' experts from testifying regarding their own Fabry Disease diagnostic practices, including requesting that a HEK Assay be run to determine migalastat amenability. Aurobindo seeks only to preclude Plaintiffs from eliciting testimony their experts have definitively admitted under oath they are not qualified to give. For the same reasons this Court excluded expert testimony in the *Withrow* case, Aurobindo respectfully submits Drs. Hopkin and Jeffries should not be permitted to testify regarding the HEK Assay at trial. Aurobindo, therefore, requests that all such testimony of theirs be precluded.

EXHIBIT 18

**AUROBINDO'S MOTION *IN LIMINE* NO. 1:
PRECLUSION/EXCLUSION OF PLAINTIFFS'
EXPERT TESTIMONY REGARDING THE HEK ASSAY**

EXHIBIT A



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Transcript of Robert J. Hopkin, M.D.

Date: June 10, 2025

Case: Amicus Therapeutics US, LLC, et al. -v- Teva Pharmaceuticals USA, Inc., et al.

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Transcript of Robert J. Hopkin, M.D.

1 (1 to 4)

Conducted on June 10, 2025

<p>1 IN THE UNITED STATES DISTRICT COURT</p> <p>2 FOR THE DISTRICT OF DELAWARE</p> <p>3 - - -</p> <p>4 AMICUS THERAPEUTICS US, : 5 LLC and AMICUS : C.A. No. 1:22-cv-01461-CJB 6 THERAPEUTICS, INC., : 7 Plaintiffs, : ANDA CASE 8 vs. : (Consolidated) 9 TEVA PHARMACEUTICALS : 10 USA, INC., and TEVA : 11 PHARMACEUTICALS, INC., : 12 et al., : 13 Defendants : 14 - - -</p> <p>15 VIDEOTAPED DEPOSITION OF ROBERT J. HOPKIN, M.D.</p> <p>16 - - -</p> <p>17 Tuesday, June 10, 2025</p> <p>18 9:04 a.m.</p> <p>19 - - -</p> <p>20 Held at the offices of:</p> <p>21 Keating Muething & Klekamp, PLL 22 One East Fourth Street, Suite 1400 23 Cincinnati, Ohio 45202</p> <p>24 Reported By: Carol A. Kirk, RMR, CSR-9139</p> <p>25</p>	<p>1 INDEX TO EXAMINATION</p> <p>2 WITNESS PAGE</p> <p>3 ROBERT J. HOPKIN, M.D.</p> <p>4 CROSS-EXAMINATION BY MR. BARRY 8</p> <p>5</p> <p>6</p> <p>7</p> <p>8</p> <p>9</p> <p>10</p> <p>11</p> <p>12</p> <p>13</p> <p>14</p> <p>15</p> <p>16</p> <p>17</p> <p>18</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p> <p>25</p>
<p>1 A P P E A R A N C E S</p> <p>2 - - -</p> <p>3 On behalf of the Plaintiffs:</p> <p>4 GROOMBRIDGE, WU, BAUGHMAN & STONE, LLP 5 BY: JENNIFER REA DENEALT, ESQUIRE 6 jenna.deneault@groombridgewu.com 7 NAZ E. WEHRLI, ESQUIRE 8 naz.wehrli@groombridgewu.com 9 KYLE N. BERSANI, ESQUIRE 10 kyle.bersani@groombridgewu.com 11 565 Fifth Avenue, Suite 2900 12 New York, New York 10017 13 332-269-0030</p> <p>14 On behalf of the Defendants, Aurobindo Pharma LTD., 15 and Aurobindo Pharma USA, Inc.:</p> <p>16 KRATZ & BARRY, LLP 17 BY: GEORGE J. BARRY, III, ESQUIRE 18 gbarry@kratzandbarry.com 19 1050 Crown Pointe Parkway, Suite 500 20 Atlanta, Georgia 30338 21 404-431-6600</p> <p>22 ALSO PRESENT:</p> <p>23 Joon Chung</p> <p>24 - - -</p> <p>25</p>	<p>1 INDEX TO EXHIBITS</p> <p>2 HOPKIN DESCRIPTION PAGE</p> <p>3 Exhibit 1 Curriculum Vitae of Robert J. Hopkin, M.D. 11</p> <p>4 Exhibit 2 Rebuttal Report of Robert J. Hopkin, M.D. 24</p> <p>5 Exhibit 3 Document titled "Molecular Genetics and Metabolism Reports" 83</p> <p>6 Exhibit 4 United States Patent Number 11,633,388 92</p> <p>7 Exhibit 5 Galafold label 93</p> <p>8 Exhibit 6 Document titled "Sapropterin dihydrochloride, 6-R-L-erythro-5,6,7,8-tetrahydrobiopterin, in the treatment of phenylketonuria" 116</p> <p>9 Exhibit 7 Document titled "Drugs@FDA: FDA-Approved Drugs" 119</p> <p>10 Exhibit 8 United States Patent Number 12,042,489 133</p> <p>11 Exhibit 9 United States Patent Number 12,042,490 133</p> <p>12 Exhibit 10 United States Patent Number 11,833,164 134</p> <p>13 Exhibit 11 United States Patent Number 8,592,362 136</p> <p>14 Exhibit 12 United States Patent Number 2011/0152319, Bates-stamped DEFMIG_0000140 through 312 156</p> <p>15 Exhibit 13 Document titled "A Pharmacogenetic Approach to Identify Mutant Forms of a-Galactosidase A that Respond to a Pharmacological Chaperone for Fabry Disease" 169</p> <p>16</p> <p>17</p> <p>18</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p> <p>25</p>

<p style="text-align: center;">5</p> <p>1 INDEX TO EXHIBITS (CON'T)</p> <p>2 HOPKIN DESCRIPTION PAGE</p> <p>3 Exhibit 14 Document titled Safety and 172</p> <p>4 pharmacodynamic effects of a</p> <p>5 pharmacological chaperone on</p> <p>6 a-galactosidase A activity and</p> <p>7 globotriaosylceramide clearance</p> <p>8 in Fabry disease: report from</p> <p>9 two phase 2 clinical studies"</p> <p>10 Exhibit 15 Document titled "Amicus 178</p> <p>11 Therapeutics Presents</p> <p>12 Additional 6-Month Results from</p> <p>13 Phase 3 Fabry Monotherapy Study</p> <p>14 at LDN World Symposium"</p> <p>15 Exhibit 16 Document titled "A Phase 2 181</p> <p>16 study of migalastat</p> <p>17 hydrochloride in females with</p> <p>18 Fabry disease: Selection of</p> <p>19 population, safety and</p> <p>20 pharmacodynamic effects"</p> <p>21 Exhibit 17 United States Patent Number 182</p> <p>22 2015/0352093</p> <p>23 Exhibit 18 Document titled "The Validation 191</p> <p>24 of Pharmacogenetics in the</p> <p>25 Identification of Target Fabry</p> <p>Patients for Treatment with</p> <p>Migalastat"</p> <p>Exhibit 19 Deposition of Elfrida Benjamin, 202</p> <p>Ph.D.</p> <p>Exhibit 20 Dr. Elfrida Benjamin Deposition 203</p> <p>Transcript Errata</p> <p>Exhibit 21 Transcript of Jeffrey P. 224</p> <p>Castelli, Ph.D., Designated</p> <p>Representative and</p> <p>Individually, dated February</p> <p>21, 2025</p> <p>Exhibit 22 Dr. Jeffrey Castelli Deposition 224</p> <p>Transcript Errata</p>	<p style="text-align: center;">7</p> <p>1 Would counsel please voice</p> <p>2 identify themselves and state whom they</p> <p>3 represent.</p> <p>4 MR. BARRY: George Barry, Kratz &</p> <p>5 Barry for Aurobindo.</p> <p>6 MS. DENEALT: Jennifer Deneault,</p> <p>7 Naz Wehrli, Kyle Bersani from</p> <p>8 Groombridge Wu on behalf of Amicus</p> <p>9 Therapeutics, and Joon Chung from Amicus</p> <p>10 Therapeutics.</p> <p>11 THE VIDEOGRAPHER: The court</p> <p>12 reporter today is Carol Kirk</p> <p>13 representing Planet Depos.</p> <p>14 The witness will now be sworn.</p> <p>15 (Witness sworn.)</p> <p>16 MS. DENEALT: And I'd like to</p> <p>17 make a comment at the outset that</p> <p>18 Dr. Hopkin is prepared to address the</p> <p>19 written description and enablement</p> <p>20 references that Dr. Medin makes in the</p> <p>21 context of obviousness in his reply</p> <p>22 expert report.</p> <p>23 MR. BARRY: Thanks.</p> <p>24 - - -</p> <p>25</p>
<p style="text-align: center;">6</p> <p>1 - - -</p> <p>2 P R O C E E D I N G S</p> <p>3 - - -</p> <p>4 THE VIDEOGRAPHER: Here begins</p> <p>5 media number 1 in the videotaped</p> <p>6 deposition of Robert J. Hopkin M.D., in</p> <p>7 the matter of Amicus Therapeutics US,</p> <p>8 LLC, et al. v. Teva Pharmaceuticals USA</p> <p>9 Inc. et al. in the United States</p> <p>10 District Court for the District of</p> <p>11 Delaware, Case Number 1:22-cv-01461-CJB.</p> <p>12 Today's date is June 10, 2025.</p> <p>13 The time on the video monitor is</p> <p>14 9:04 a.m. Eastern Standard Time.</p> <p>15 The remote videographer -- I'm</p> <p>16 sorry. The regular videographer today</p> <p>17 is Michael Harden representing Planet</p> <p>18 Depos.</p> <p>19 All parties of this video</p> <p>20 deposition are attending at the law</p> <p>21 offices -- sorry. I lost my place.</p> <p>22 Stand by.</p> <p>23 All parties are attending at the</p> <p>24 law offices of Keating Muething &</p> <p>25 Klecamp PLL.</p>	<p style="text-align: center;">8</p> <p>1 ROBERT J. HOPKIN, M.D.</p> <p>2 being by me first duly sworn, as hereinafter</p> <p>3 certified, deposes and says as follows:</p> <p>4 CROSS-EXAMINATION</p> <p>5 BY MR. BARRY:</p> <p>6 Q. Good morning, Dr. Hopkin.</p> <p>7 A. Good morning.</p> <p>8 Q. We met briefly. I'm George Barry.</p> <p>9 I represent Aurobindo in this case.</p> <p>10 Thank you for being with us here</p> <p>11 today.</p> <p>12 Before we get started, have you ever</p> <p>13 been deposed before?</p> <p>14 A. Yes, I have.</p> <p>15 Q. About how many times?</p> <p>16 A. I don't remember.</p> <p>17 Q. Is it more than ten?</p> <p>18 A. No. Probably less than ten.</p> <p>19 Q. When was the last time you were</p> <p>20 deposed?</p> <p>21 A. I don't remember that either.</p> <p>22 Q. Was it in the last five years?</p> <p>23 A. Yes.</p> <p>24 Q. Okay. Do you remember what -- what</p> <p>25 you have in mind? What the nature of your</p>

Conducted on June 10, 2025

<p>65</p> <p>1 [REDACTED]</p> <p>2 [REDACTED]</p> <p>3 [REDACTED]</p> <p>4 [REDACTED]</p> <p>5 [REDACTED]</p> <p>6 [REDACTED]</p> <p>7 [REDACTED]</p> <p>8 [REDACTED]</p> <p>9 [REDACTED]</p> <p>10 [REDACTED]</p> <p>11 [REDACTED]</p> <p>12 [REDACTED]</p> <p>13 [REDACTED]</p> <p>14 [REDACTED]</p> <p>15 [REDACTED]</p> <p>16 [REDACTED]</p> <p>17 [REDACTED]</p> <p>18 [REDACTED]</p> <p>19 [REDACTED]</p> <p>20 [REDACTED]</p> <p>21 [REDACTED]</p> <p>22 [REDACTED]</p> <p>23 [REDACTED]</p> <p>24 [REDACTED]</p> <p>25 [REDACTED]</p>	<p>67</p> <p>1 Q. Meaning after FDA approval in 2018?</p> <p>2 A. It would -- in any setting, so it</p> <p>3 could -- I mean, in patient setting in the</p> <p>4 clinical trials would have been evaluated as well.</p> <p>5 Q. Well, that was part of the clinical</p> <p>6 trials, right, was evaluating the patients?</p> <p>7 A. Right. The patients had to -- in</p> <p>8 order to enroll in the clinical trial, the</p> <p>9 patients had to have that testing done.</p> <p>10 Q. Do you remember when you started</p> <p>11 admitting patients for the earliest clinical trial</p> <p>12 that you had found regarding migalastat?</p> <p>13 A. I do not remember.</p> <p>14 Q. Do you know when Amicus -- strike</p> <p>15 that.</p> <p>16 Prior to that time, prior to you</p> <p>17 beginning enrolling patients for a study for</p> <p>18 migalastat, did you have any patients evaluated</p> <p>19 for migalastat amenability?</p> <p>20 A. I don't think so.</p> <p>21 Q. Have you ever run a HEK assay?</p> <p>22 A. I don't have a lab, so no.</p> <p>23 Q. What is a HEK assay?</p> <p>24 A. It is a method for assessing the</p> <p>25 response -- in this case, the response of the</p>
<p>66</p> <p>1 [REDACTED]</p> <p>2 So sitting here today, you do not</p> <p>3 have an understanding as to the basis for the EU's</p> <p>4 approval of migalastat prior to 2012; is that</p> <p>5 correct?</p> <p>6 A. That is correct.</p> <p>7 Q. I may have already tried to test</p> <p>8 your memory on this one, but I apologize if that</p> <p>9 is true.</p> <p>10 Do you remember approximately -- oh,</p> <p>11 yeah, I think you said that your first patient was</p> <p>12 in 1991?</p> <p>13 A. 1997.</p> <p>14 Q. 1997.</p> <p>15 And so when was the first time you</p> <p>16 sought to determine whether one of your patients</p> <p>17 would be amenable to migalastat?</p> <p>18 A. Honestly, I don't remember.</p> <p>19 Q. Do you know whether that would have</p> <p>20 been in connection with a study that you were</p> <p>21 working on, or would it have been before that?</p> <p>22 A. I was aware of the concept of</p> <p>23 amenability before that, but I didn't have any</p> <p>24 reason to pursue that until it became a potential</p> <p>25 option for a patient.</p>	<p>68</p> <p>1 cells to migalastat.</p> <p>2 Q. Do you know how to perform an HEK</p> <p>3 assay?</p> <p>4 A. I don't perform a HEK assay, so</p> <p>5 I don't feel I can -- so, no, I don't feel</p> <p>6 confident in doing that.</p> <p>7 Q. Do you have an understanding of the</p> <p>8 steps needed to perform a HEK assay?</p> <p>9 A. Not in detail.</p> <p>10 Q. And is that the true of the GLP-HEK</p> <p>11 assay as well?</p> <p>12 A. Yes.</p> <p>13 Q. And is that true of the R&D HEK</p> <p>14 assay?</p> <p>15 A. It's true for the HEK assay.</p> <p>16 [REDACTED]</p> <p>17 [REDACTED]</p> <p>18 [REDACTED]</p> <p>19 [REDACTED]</p> <p>20 [REDACTED]</p> <p>21 [REDACTED]</p> <p>22 [REDACTED]</p> <p>23 [REDACTED]</p> <p>24 [REDACTED]</p> <p>25 [REDACTED]</p>

Conducted on June 10, 2025

<p>69</p> <p>1 [REDACTED]</p> <p>2 [REDACTED]</p> <p>3 [REDACTED]</p> <p>4 [REDACTED]</p> <p>5 [REDACTED]</p> <p>6 [REDACTED]</p> <p>7 [REDACTED]</p> <p>8 [REDACTED]</p> <p>9 [REDACTED]</p> <p>10 [REDACTED]</p> <p>11 [REDACTED]</p> <p>12 [REDACTED]</p> <p>13 [REDACTED]</p> <p>14 [REDACTED]</p> <p>15 [REDACTED]</p> <p>16 [REDACTED]</p> <p>17 [REDACTED]</p> <p>18 [REDACTED]</p> <p>19 [REDACTED]</p> <p>20 [REDACTED]</p> <p>21 [REDACTED]</p> <p>22 [REDACTED]</p> <p>23 [REDACTED]</p> <p>24 [REDACTED]</p> <p>25 [REDACTED]</p>	<p>71</p> <p>1 [REDACTED]</p> <p>2 [REDACTED]</p> <p>3 [REDACTED]</p> <p>4 [REDACTED]</p> <p>5 [REDACTED]</p> <p>6 [REDACTED]</p> <p>7 [REDACTED]</p> <p>8 [REDACTED]</p> <p>9 [REDACTED]</p> <p>10 [REDACTED]</p> <p>11 [REDACTED]</p> <p>12 [REDACTED]</p> <p>13 [REDACTED]</p> <p>14 [REDACTED]</p> <p>15 [REDACTED]</p> <p>16 [REDACTED]</p> <p>17 [REDACTED]</p> <p>18 [REDACTED]</p> <p>19 [REDACTED]</p> <p>20 [REDACTED]</p> <p>21 [REDACTED]</p> <p>22 [REDACTED]</p> <p>23 [REDACTED]</p> <p>24 [REDACTED]</p> <p>25 [REDACTED]</p>
<p>70</p> <p>1 [REDACTED]</p> <p>2 [REDACTED]</p> <p>3 [REDACTED]</p> <p>4 [REDACTED]</p> <p>5 [REDACTED]</p> <p>6 [REDACTED]</p> <p>7 [REDACTED]</p> <p>8 [REDACTED]</p> <p>9 [REDACTED]</p> <p>10 [REDACTED]</p> <p>11 [REDACTED]</p> <p>12 [REDACTED]</p> <p>13 [REDACTED]</p> <p>14 [REDACTED]</p> <p>15 [REDACTED]</p> <p>16 [REDACTED]</p> <p>17 [REDACTED]</p> <p>18 [REDACTED]</p> <p>19 [REDACTED]</p> <p>20 [REDACTED]</p> <p>21 [REDACTED]</p> <p>22 [REDACTED]</p> <p>23 [REDACTED]</p> <p>24 [REDACTED]</p> <p>25 [REDACTED]</p>	<p>72</p> <p>1 [REDACTED]</p> <p>2 [REDACTED]</p> <p>3 [REDACTED]</p> <p>4 [REDACTED]</p> <p>5 [REDACTED]</p> <p>6 [REDACTED]</p> <p>7 [REDACTED]</p> <p>8 [REDACTED]</p> <p>9 [REDACTED]</p> <p>10 [REDACTED]</p> <p>11 [REDACTED]</p> <p>12 [REDACTED]</p> <p>13 [REDACTED]</p> <p>14 [REDACTED]</p> <p>15 [REDACTED]</p> <p>16 Q. Do you -- in your report that you</p> <p>17 prepared, do you discuss the differences between</p> <p>18 the assays?</p> <p>19 A. Not in any detail.</p> <p>20 [REDACTED]</p> <p>21 [REDACTED]</p> <p>22 [REDACTED]</p> <p>23 [REDACTED]</p> <p>24 [REDACTED]</p> <p>25 Q. Do you know when Amicus made -- or</p>

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<p>77</p> <p>1 [REDACTED]</p> <p>2 [REDACTED]</p> <p>3 [REDACTED]</p> <p>4 [REDACTED]</p> <p>5 [REDACTED]</p> <p>6 [REDACTED]</p> <p>7 [REDACTED]</p> <p>8 [REDACTED]</p> <p>9 [REDACTED]</p> <p>10 [REDACTED]</p> <p>11 [REDACTED]</p> <p>12 [REDACTED]</p> <p>13 [REDACTED]</p> <p>14 [REDACTED]</p> <p>15 [REDACTED]</p> <p>16 [REDACTED]</p> <p>17 [REDACTED]</p> <p>18 [REDACTED]</p> <p>19 [REDACTED]</p> <p>20 [REDACTED]</p> <p>21 [REDACTED]</p> <p>22 [REDACTED]</p> <p>23 [REDACTED]</p> <p>24 [REDACTED]</p> <p>25 [REDACTED]</p>	<p>79</p> <p>1 [REDACTED]</p> <p>2 [REDACTED]</p> <p>3 [REDACTED]</p> <p>4 [REDACTED]</p> <p>5 [REDACTED]</p> <p>6 [REDACTED]</p> <p>7 [REDACTED]</p> <p>8 [REDACTED]</p> <p>9 [REDACTED]</p> <p>10 [REDACTED]</p> <p>11 [REDACTED]</p> <p>12 [REDACTED]</p> <p>13 [REDACTED]</p> <p>14 [REDACTED]</p> <p>15 [REDACTED]</p> <p>16 [REDACTED]</p> <p>17 [REDACTED]</p> <p>18 [REDACTED]</p> <p>19 [REDACTED]</p> <p>20 [REDACTED]</p> <p>21 [REDACTED]</p> <p>22 [REDACTED]</p> <p>23 [REDACTED]</p> <p>24 [REDACTED]</p> <p>25 [REDACTED]</p>
<p>78</p> <p>1 [REDACTED]</p> <p>2 [REDACTED]</p> <p>3 [REDACTED]</p> <p>4 [REDACTED]</p> <p>5 [REDACTED]</p> <p>6 [REDACTED]</p> <p>7 [REDACTED]</p> <p>8 [REDACTED]</p> <p>9 [REDACTED]</p> <p>10 [REDACTED]</p> <p>11 [REDACTED]</p> <p>12 [REDACTED]</p> <p>13 [REDACTED]</p> <p>14 [REDACTED]</p> <p>15 [REDACTED]</p> <p>16 [REDACTED]</p> <p>17 [REDACTED]</p> <p>18 [REDACTED]</p> <p>19 [REDACTED]</p> <p>20 [REDACTED]</p> <p>21 [REDACTED]</p> <p>22 [REDACTED]</p> <p>23 [REDACTED]</p> <p>24 [REDACTED]</p> <p>25 [REDACTED]</p>	<p>80</p> <p>1 MR. BARRY: Let's take a break.</p> <p>2 Let's go off the record.</p> <p>3 THE VIDEOGRAPHER: Stand by.</p> <p>4 Going off the video record. The</p> <p>5 time is 11:16 a.m.</p> <p>6 (Recess taken.)</p> <p>7 THE VIDEOGRAPHER: We are back on</p> <p>8 the video record. The time is</p> <p>9 11:28 a.m.</p> <p>10 BY MR. BARRY:</p> <p>11 Q. Doctor, welcome back.</p> <p>12 [REDACTED]</p> <p>13 [REDACTED]</p> <p>14 [REDACTED]</p> <p>15 [REDACTED]</p> <p>16 [REDACTED]</p> <p>17 [REDACTED]</p> <p>18 [REDACTED]</p> <p>19 [REDACTED]</p> <p>20 [REDACTED]</p> <p>21 [REDACTED]</p> <p>22 [REDACTED]</p> <p>23 [REDACTED]</p> <p>24 [REDACTED]</p> <p>25 [REDACTED]</p>

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<p>113</p> <p>1 Q. Do you understand how to run a HEK 2 assay? 3 A. Not in detail. 4 Q. Would a POSA understand the details 5 of conducting a HEK assay? 6 A. That depends on the background of 7 the POSA. 8 Q. Well, in your definition of a POSA, 9 would a POSA understand the details of running a 10 HEK assay? 11 A. So in my definition, and as I said 12 just a few minutes ago, a person can be a POSA and 13 not have to be in a laboratory or working in a 14 laboratory setting. The person could also be a 15 POSA and work in a laboratory setting. 16 Presumably the people who work in a 17 laboratory setting either using a clinical assay 18 that involves the HEK assay, or a clinical 19 assessment that involves the HEK assay, or as a 20 researcher who uses HEK assays would understand 21 that because that's part of their role, but one 22 could also be a POSA and not understand the 23 details of running a HEK assay. 24 Similarly, somebody could be a POSA 25 and not know -- not see patients, not understand</p>	<p>115</p> <p>1 THE VIDEOGRAPHER: Stand by. 2 Going off the video record. The 3 time is 12:28 p.m. 4 --- 5 (Thereupon, at 12:28 p.m. a lunch recess 6 was taken until 1:19 p.m.) 7 --- 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25</p>
<p>114</p> <p>1 all of the details of the clinical assessment of 2 the patient, because in Fabry disease, they would 3 need to have expertise in some other aspect of 4 this process. 5 Q. We're kind of shifting gears here. 6 Thinking about the patents that you 7 reviewed for the purpose of your report, the 8 reassessment patents, the '388, '489 and '490 9 patents -- you know what I'm referring to? 10 A. Yes. 11 Q. Is it your understanding that they 12 have a common specification? 13 A. I would have to look at the details. 14 Q. I'm guessing you'll want to look at 15 them. 16 MR. BARRY: We're going to go 17 ahead and mark -- actually, you know 18 what? Maybe, Counsel, this would be a 19 good time to take a break -- 20 MS. DENEALT: Sure. 21 MR. BARRY: -- since we're 22 shifting gears. 23 MS. DENEALT: Sure. 24 MR. BARRY: I'll get some exhibits 25 marked.</p>	<p>116</p> <p>1 Tuesday Afternoon Session 2 June 10, 2025 3 1:19 p.m. 4 --- 5 THE VIDEOGRAPHER: We are back on 6 video record. The time is 1:19 p.m. 7 BY MR. BARRY: 8 Q. Dr. Hopkin, welcome back. 9 Earlier we talked about 10 pharmacological chaperones, and you had testified 11 that migalastat was the first pharmacological 12 chaperone FDA approved for Fabry disease; is that 13 correct? 14 A. Yes. 15 --- 16 (Hopkin Deposition Exhibit 6 marked.) 17 --- 18 BY MR. BARRY: 19 Q. All right. Doctor, you've been 20 handed what has been marked as Exhibit 6. 21 Do you recognize this document, 22 Exhibit 6, as an abstract, a publication abstract? 23 A. Yes. 24 Q. And this is a publication abstract 25 titled "Sapropterin dihydrochloride, 26 6-R-L-erythro-5,6,7,8-tetrahydrobiopterin, in the</p>

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<p style="text-align: right;">165</p> <p>1 paragraph 47 into the record?</p> <p>2 A. "In one specific embodiment, the</p> <p>3 invention provides methods for determining whether</p> <p>4 an SPC enhances enzyme activity of a mutant</p> <p>5 alpha-galactosidase A enzyme and can, therefore,</p> <p>6 be utilized as an effective therapeutic treatment</p> <p>7 for a Fabry disease patient expressing the same</p> <p>8 alpha-galactosidase A mutation."</p> <p>9 Q. And at least based on the</p> <p>10 information that was available in June of 2011,</p> <p>11 would a POSA have had any reason to disagree with</p> <p>12 that?</p> <p>13 A. So based on the information that was</p> <p>14 available in 2011, a POSA would have had reason</p> <p>15 not to disagree with it but to question it.</p> <p>16 Q. Well, there's always reason to</p> <p>17 question pretty much everything, right?</p> <p>18 A. There's lots of reasons to ask</p> <p>19 questions, yes.</p> <p>20 Q. I have to apologize. I hate asking</p> <p>21 people to read stuff into the record. It seems</p> <p>22 cruel. I don't meant to. I may have a couple</p> <p>23 more about that.</p> <p>24 So, yeah, looking at the page ending</p> <p>25 in Bates number 212.</p>	<p style="text-align: right;">167</p> <p>1 disease. It's a biomarker rather than a clinical</p> <p>2 correlation.</p> <p>3 Q. So when you would describe a</p> <p>4 clinical correlation, you're not referring</p> <p>5 necessarily to a diagnostic exam of a patient; is</p> <p>6 that right?</p> <p>7 A. So when I'm describing a clinical</p> <p>8 correlation, it means something that I can see or</p> <p>9 measure that's functionally important to the</p> <p>10 patient in an immediate sense.</p> <p>11 And a biomarker is something that's</p> <p>12 chemically outside of the normal range but may or</p> <p>13 may not have an immediate impact on health.</p> <p>14 So in this case, the low enzyme</p> <p>15 level, if it stays low throughout life, it will</p> <p>16 eventually lead to problems, but a measurement at</p> <p>17 that time doesn't tell you anything about how that</p> <p>18 patient is doing at that moment.</p> <p>19 And the descriptions that we have</p> <p>20 just read are looking at the manifestations of the</p> <p>21 biochemical activity of the enzyme and not at the</p> <p>22 condition of the patient or any evidence of damage</p> <p>23 to organs that are typically impacted by Fabry</p> <p>24 disease.</p> <p>25 Q. So you would agree they're</p>
<p style="text-align: right;">166</p> <p>1 A. In which document?</p> <p>2 Q. It's the same document.</p> <p>3 A. Okay.</p> <p>4 Q. So Exhibit 12.</p> <p>5 A. Which part of that page?</p> <p>6 Q. Looking at paragraph 147 under the</p> <p>7 word "Conclusion."</p> <p>8 A. Okay.</p> <p>9 Q. Could I ask you to please read</p> <p>10 paragraph 147 into the record.</p> <p>11 A. "These described results are</p> <p>12 comparable to those obtained from Fabry</p> <p>13 patient-derived lymphoid or T-cells, as well as</p> <p>14 the alpha-galactosidase A enzyme responses</p> <p>15 observed in white blood cells of Fabry patients</p> <p>16 after oral administration of DGJ in Phase 2</p> <p>17 clinical trials."</p> <p>18 Q. So do you agree here they're</p> <p>19 describing a clinical correlation with their assay</p> <p>20 results?</p> <p>21 A. No, I do not agree with that.</p> <p>22 Q. Why not?</p> <p>23 A. Because this is a biochemical assay,</p> <p>24 and they're looking at the measured enzyme</p> <p>25 activity, not a clinical manifestation of Fabry</p>	<p style="text-align: right;">168</p> <p>1 identifying a correlation between the assay and</p> <p>2 biomarker; is that fair?</p> <p>3 A. Right.</p> <p>4 Q. Okay. Can you read 148 into the</p> <p>5 record.</p> <p>6 A. "Thus, the GripTite 293 MSR</p> <p>7 transient transfection assay is a reliable method</p> <p>8 for identifying DGJ responsive mutations</p> <p>9 characterizing the magnitude and potency of this</p> <p>10 response."</p> <p>11 Q. Thank you.</p> <p>12 Do you understand that GripTite 293</p> <p>13 MSR transient transfection assay to be another way</p> <p>14 to describe the R&D HEK assay we've been talking</p> <p>15 about?</p> <p>16 A. That is my impression.</p> <p>17 Q. Is GripTite -- is that a trademark?</p> <p>18 A. I don't know where GripTite comes</p> <p>19 from.</p> <p>20 Q. Does that suggest that Amicus did</p> <p>21 not develop the GripTite 293 MSR transient</p> <p>22 transfection assay?</p> <p>23 A. I don't know.</p> <p>24 Q. Do you know who developed the R&D</p> <p>25 HEK assay?</p>

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<p>169</p> <p>1 A. I do not.</p> <p>2 Q. Do you know whether Amicus developed</p> <p>3 the R&D HEK assay?</p> <p>4 A. I just said I don't know who</p> <p>5 developed it.</p> <p>6 Q. Yeah, but you might know who didn't.</p> <p>7 So do you know whether Amicus did not?</p> <p>8 A. I don't know.</p> <p>9 Q. We can set that one aside. Let's</p> <p>10 move on to the next.</p> <p>11 ---</p> <p>12 (Hopkin Deposition Exhibit 13 marked.)</p> <p>13 ---</p> <p>14 BY MR. BARRY:</p> <p>15 Q. Dr. Hopkin, you've been handed what</p> <p>16 has been marked as Exhibit 13.</p> <p>17 Do you recognize Exhibit 13 as the</p> <p>18 Wu reference that Aurobindo has cited as a priori</p> <p>19 against the patents ensued?</p> <p>20 A. Yes.</p> <p>21 Q. This is a Wu reference that is</p> <p>22 discussed in your report, correct?</p> <p>23 A. Correct.</p> <p>24 Q. And Wu is discussing the R&D HEK</p> <p>25 assay, correct?</p>	<p>171</p> <p>1 it and let me know when you're done.</p> <p>2 So is it your opinion that the Wu</p> <p>3 reference would not give a POSA any motivation to</p> <p>4 try the R&D HEK assay to identify or determine</p> <p>5 whether a mutation is amenable to migalastat?</p> <p>6 A. Can you give a little more context?</p> <p>7 Q. Well, is it -- I'm not sure what</p> <p>8 context you need. I'm asking you about your</p> <p>9 understanding of Wu.</p> <p>10 You've stated in your report that</p> <p>11 persons of ordinary skill in the art would not be</p> <p>12 motivated to use the R&D HEK assay.</p> <p>13 So does Wu not provide any -- is it</p> <p>14 your opinion that Wu does not provide a POSA with</p> <p>15 any motivation to try an R&D HEK assay to</p> <p>16 determine amenability?</p> <p>17 A. I am still not following where</p> <p>18 you're going with this.</p> <p>19 Wu gives -- I mean, the conclusion</p> <p>20 states that they found some consistency in</p> <p>21 response. They also note in the paper that they</p> <p>22 identified a number of mutations and how they</p> <p>23 responded. So would one use this data and say,</p> <p>24 "Is this mutation amenable?" Yes.</p> <p>25 Beyond that, I'm not sure what, you</p>
<p>170</p> <p>1 A. Presumably, yes.</p> <p>2 Q. Do you know what AT1001 refers to?</p> <p>3 A. It's migalastat. I think the other</p> <p>4 one that you referenced earlier is at least a very</p> <p>5 similar molecule. It's related, but I don't</p> <p>6 know --</p> <p>7 Q. You're talking about the 1-deoxy- --</p> <p>8 the crazy one?</p> <p>9 A. Yeah.</p> <p>10 Q. Thank you.</p> <p>11 And your recollection now is that</p> <p>12 you think that also is migalastat?</p> <p>13 A. I think it's at least a very similar</p> <p>14 molecule.</p> <p>15 Q. Understood. Thanks.</p> <p>16 So I'm looking at Wu at page 976.</p> <p>17 It's the page with the Bates number ending 1131.</p> <p>18 And for the record, this one bears</p> <p>19 Bates number DEFMIG_0001119 through 1132.</p> <p>20 So are you at page 1131 with me,</p> <p>21 Doctor?</p> <p>22 A. Yes.</p> <p>23 Q. Just above Acknowledgments, there's</p> <p>24 a paragraph or a conclusion. If you could read</p> <p>25 that paragraph. Not into the record. Just read</p>	<p>172</p> <p>1 know -- under what -- with what goal or what</p> <p>2 circumstances -- what application are you looking</p> <p>3 for for that knowledge, because that would be</p> <p>4 important for where you would use it.</p> <p>5 Q. Paragraph 44 of your report is</p> <p>6 discussing the Germain reference. Excuse me. I'm</p> <p>7 sorry. Paragraph 111. In paragraph 111 of your</p> <p>8 report, you discuss the Germain reference starting</p> <p>9 at paragraph 109.</p> <p>10 A. Okay.</p> <p>11 Q. All right. Continuing through 113.</p> <p>12 ---</p> <p>13 (Hopkin Deposition Exhibit 14 marked.)</p> <p>14 ---</p> <p>15 BY MR. BARRY:</p> <p>16 Q. Dr. Hopkin, the document that's been</p> <p>17 handed to you is marked as Exhibit 16 and bears</p> <p>18 the Bates number --</p> <p>19 THE COURT REPORTER: 14.</p> <p>20 MR. BARRY: Excuse me. What's</p> <p>21 that?</p> <p>22 THE COURT REPORTER: 14.</p> <p>23 THE WITNESS: 14.</p> <p>24 MR. BARRY: 14. All right. I'll</p> <p>25 try it again.</p>

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<p>193</p> <p>1 [REDACTED]</p> <p>2 [REDACTED]</p> <p>3 [REDACTED]</p> <p>4 [REDACTED]</p> <p>5 [REDACTED]</p> <p>6 [REDACTED]</p> <p>7 [REDACTED]</p> <p>8 [REDACTED]</p> <p>9 [REDACTED]</p> <p>10 [REDACTED]</p> <p>11 [REDACTED]</p> <p>12 Q. So if we look down at that same</p> <p>13 page, looking at page 2 of the Bates number ending</p> <p>14 in 585, in the fourth cell down where the heading</p> <p>15 says "Data from Phase 3 Study AT1001-011."</p> <p>16 Do you see that?</p> <p>17 A. Yes.</p> <p>18 Q. That's a reference to the 011 study</p> <p>19 that we've discussed today?</p> <p>20 A. Yes.</p> <p>21 Q. And if we look in that cell under</p> <p>22 "Key Inclusion Criteria," the second bullet after</p> <p>23 that, can you read that into the record for me,</p> <p>24 the second bullet after "Key Inclusion Criteria"?</p> <p>25 A. "Amenable GLA mutation during</p>	<p>195</p> <p>1 A. Yes.</p> <p>2 Q. They are describing the R&D HEK</p> <p>3 assay as preliminary, correct?</p> <p>4 A. Correct.</p> <p>5 Q. Does Benjamin say anything else</p> <p>6 about the R&D HEK assay, Benjamin 2016?</p> <p>7 A. In the next page, it has a box</p> <p>8 entitled "Migalastat Amenability Assay Procedure</p> <p>9 and Data Overview."</p> <p>10 Q. And is this a description of the R&D</p> <p>11 HEK assay?</p> <p>12 A. I don't know. It's an amenability</p> <p>13 assay.</p> <p>14 Q. Are you familiar enough with the R&D</p> <p>15 HEK assay and the GLP-HEK assay to look at that</p> <p>16 diagram and distinguish them?</p> <p>17 A. Honestly, my eyes are not good</p> <p>18 enough to look at that diagram and be able to read</p> <p>19 all of the details.</p> <p>20 Q. How about in the description below</p> <p>21 the diagrams, the words describing it?</p> <p>22 A. So it doesn't give all of the</p> <p>23 details of the assay, and it doesn't specify which</p> <p>24 version.</p> <p>25 Q. Well, but this publication is really</p>
<p>194</p> <p>1 screening the GLA mutation was confirmed by gene</p> <p>2 sequencing. The amenable category was determined</p> <p>3 by a preliminary HEK-293 cell-based assay.</p> <p>4 Q. And that's a reference to the R&D</p> <p>5 HEK assay, correct?</p> <p>6 A. Yes.</p> <p>7 Q. And here again, the inventors in</p> <p>8 this case are describing the R&D HEK assay as</p> <p>9 preliminary, right?</p> <p>10 A. Correct.</p> <p>11 Q. They're not describing it as</p> <p>12 inaccurate, right?</p> <p>13 A. Correct.</p> <p>14 Q. Now, we go down to the next cell</p> <p>15 down under the heading "Data from Phase 3 Study</p> <p>16 AT1001-012."</p> <p>17 Do you see that?</p> <p>18 A. Yes.</p> <p>19 Q. Okay. And that's a reference to the</p> <p>20 012 study that you identify in your report?</p> <p>21 A. Correct.</p> <p>22 Q. All right. And the same thing under</p> <p>23 "Key Inclusion Criteria," they have the identical</p> <p>24 statement in the second bullet point as the one</p> <p>25 you just read, correct?</p>	<p>196</p> <p>1 about the GLP-HEK assay, right? Don't they</p> <p>2 describe it --</p> <p>3 A. Yes.</p> <p>4 Q. -- as migalastat amenability assay?</p> <p>5 A. Yes. So it's presumably the GLP.</p> <p>6 Q. Yeah. So that seems like it's a</p> <p>7 description of the GLP-HEK assay, but do you</p> <p>8 know -- just looking at that description in that</p> <p>9 bullet point, in that cell, can you tell me what</p> <p>10 you would point to as what's different in that</p> <p>11 description and what you understand to be the case</p> <p>12 with the R&D HEK assay?</p> <p>13 A. I have said before that I'm not the</p> <p>14 person who runs the lab, and I don't feel</p> <p>15 comfortable describing the details and trying to</p> <p>16 pick apart the documented descriptions.</p> <p>17 Q. I think we got sidetracked there.</p> <p>18 I had asked you originally if there</p> <p>19 was anything else in this about the R&D HEK assay,</p> <p>20 and we stopped at the top cell on page 3.</p> <p>21 I wasn't sure if you had reviewed the whole</p> <p>22 document yet, and so I just wanted to give you</p> <p>23 that chance.</p> <p>24 Is there anything else about the R&D</p> <p>25 HEK assay in this document?</p>

EXHIBIT 18

**AUROBINDO'S MOTION *IN LIMINE* NO. 1:
PRECLUSION/EXCLUSION OF PLAINTIFFS'
EXPERT TESTIMONY REGARDING THE HEK ASSAY**

EXHIBIT B



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Transcript of John L. Jefferies, M.D.

Date: June 26, 2025

Case: Amicus Therapeutics US, LLC, et al. -v- Aurobindo Pharma, Ltd., et al.

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Transcript of John L. Jefferies, M.D.

1 (1 to 4)

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<p>1 UNITED STATES DISTRICT COURT</p> <p>2 THE DISTRICT OF DELAWARE</p> <p>3 -----X</p> <p>4 AMICUS THERAPEUTICS US, LLC</p> <p>5 and AMICUS THERAPEUTICS, INC.,</p> <p>6 Plaintiffs,</p> <p>7 v. C.A. No.</p> <p>8 AUROBINDO PHARMA LTD., AND 1:22-cv-01461-CFC</p> <p>9 AUROBINDO PHARMA USA, INC.,</p> <p>10 Defendants.</p> <p>11 -----X</p> <p>12</p> <p>13 DEPOSITION OF JOHN L. JEFFERIES</p> <p>14 June 26, 2025</p> <p>15</p> <p>16</p> <p>17</p> <p>18 Reported by:</p> <p>19 MARY F. BOWMAN, RPR, CRR</p> <p>20 JOB NO. 589348</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p> <p>25</p>	<p>3</p> <p>1 APPEARANCES:</p> <p>2</p> <p>3 GROOMBRIDGE, WU, BAUGHMAN & STONE LLP</p> <p>4 Attorneys for Plaintiffs</p> <p>5 565 Fifth Avenue, Suite 2900</p> <p>6 New York, New York 10017</p> <p>7 BY: JENNIFER REA DENAULT, ESQ.</p> <p>8 HAYLEY LEBLANC, ESQ.</p> <p>9 CARISSMA MCGEE, ESQ.</p> <p>10</p> <p>11</p> <p>12 KRATZ & BARRY, LLP</p> <p>13 Attorneys for Defendants</p> <p>14 1050 Crown Pointe Parkway, Suite 500</p> <p>15 Atlanta, Georgia 30338</p> <p>16 BY: GEORGE J. BARRY III, ESQ.</p> <p>17</p> <p>18 Also Present:</p> <p>19 Joon Chung, Amicus Therapeutics</p> <p>20 Robert Palos, Legal Videographer</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p> <p>25</p>
<p>2</p> <p>1</p> <p>2</p> <p>3</p> <p>4 June 26, 2025</p> <p>5 9:00 a.m.</p> <p>6</p> <p>7</p> <p>8 Deposition of JOHN L. JEFFERIES, held</p> <p>9 at Groombridge, Wu, Baughman & Stone LLP, 565</p> <p>10 Fifth Avenue Suite 2900 New York, New</p> <p>11 York, before Mary F. Bowman, a Registered</p> <p>12 Professional Reporter, Certified Realtime</p> <p>13 Reporter, and Notary Public of the States of New</p> <p>14 Jersey and New York.</p> <p>15</p> <p>16</p> <p>17</p> <p>18</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p> <p>25</p>	<p>4</p> <p>1 THE VIDEOGRAPHER: Here begins media</p> <p>2 number 1 in the videotaped deposition of</p> <p>3 John L. Jefferies, M.D., in the matter of</p> <p>4 Amicus Therapeutics US, LLC, et al.,</p> <p>5 versus Aurobindo Pharma LTD, et al., in</p> <p>6 the United States District Court for the</p> <p>7 District of Delaware, Case Number</p> <p>8 1:22-cv-01461-CFC, and 1:22-cv-01461-CJB.</p> <p>9 Today's date is June 26, 2025. The</p> <p>10 time on the monitor is 9:01 a.m.</p> <p>11 The videographer today is Robert</p> <p>12 Palos representing Planet Depos.</p> <p>13 The video deposition is taking place</p> <p>14 at 565 Fifth Avenue, New York, New York.</p> <p>15 Would counsel please voice-identify</p> <p>16 themselves and state whom they represent.</p> <p>17 (Whereupon, counsel placed their</p> <p>18 appearances on the audio record.)</p> <p>19 THE VIDEOGRAPHER: The court</p> <p>20 reporter today is Mary Bowman representing</p> <p>21 Planet Depos.</p> <p>22 The witness will now be sworn in.</p> <p>23 - - -</p> <p>24</p> <p>25</p>

Conducted on June 26, 2025

<p>5</p> <p>1 JOHN L. JEFFERIES, 2 called as a witness by the defendants, 3 having been duly sworn, testified as 4 follows: 5 EXAMINATION BY 6 MR. BARRY: 7 Q. Good morning, Dr. Jefferies. 8 A. Good morning, sir. 9 Q. I briefly introduced myself earlier. 10 I'm George Barry. I represent Aurobindo. Thank 11 you for being with us here today. 12 I'm just going to get started with 13 some questions. 14 When did the need for a migalastat 15 treatment for Fabry patients with the Y184S 16 mutation begin in your opinion? 17 A. Well, I would -- that's in my 18 statements that I submitted for review. If 19 possible, we could through those together. 20 Q. Do you recall offering an opinion 21 specifically about when a need for migalastat 22 treatment for the Y184S mutation began in your 23 opinions? 24 A. As I said, it's in my statement. I 25 would be happy to review those with you, sir.</p>	<p>7</p> <p>1 being or would it be -- would the need for 2 migalastat arise later? 3 A. In my opinion, the need for 4 migalastat would be based on if the mutation 5 that we're referencing, which could be agnostic, 6 was felt to be amenable to the therapy with 7 migalastat. 8 Q. So if I understand your testimony, 9 it is your opinion that the need for migalastat 10 therapy for a particular mutation would not 11 arise until that mutation was identified as 12 amenable for treatment with migalastat, is that 13 correct? 14 A. Well -- 15 MS. DENEALT: Objection to form. 16 A. I'm sorry. 17 Q. You can answer the question. 18 A. No, that's fine. 19 Q. No, you have to answer the question. 20 Sorry. Unless she tells you not to answer the 21 question, you have to answer the question. 22 A. Okay. 23 I think the unmet need was there 24 prior to any recognition of the mutation per se 25 as far as particular opportunities in patients.</p>
<p>6</p> <p>1 Q. So you believe that in your 2 statement, in your opinions, that you have 3 actually offered an opinion as to when the need 4 for migalastat treatment for the Y184S mutation 5 began? 6 A. I offered an opinion about an unmet 7 need specific to mutations that were approved in 8 the migalastat initial submission, yes, sir. I 9 offered an opinion about the unmet need. 10 Q. And what I'm asking about is when 11 the need arose, not necessarily when the unmet 12 need was recognized. 13 So for any of the mutations that are 14 in the asserted claims, what in your opinion 15 would be -- when did the need for a migalastat 16 treatment for those mutations arise in your 17 opinion? 18 A. Once again, I mean, we can refer to 19 my submissions and go through those line by line 20 if you would like, sir. 21 Perhaps I'm not completely 22 understanding what you're asking me. 23 Q. Well, would the need for migalastat 24 for a particular mutation, would it arise when 25 the mutation first presented itself in a human</p>	<p>8</p> <p>1 But for migalastat particularly, the indications 2 are for approved mutations that are amenable to 3 migalastat therapy. 4 Q. So if I try to break that down a 5 little bit, if I understand correctly, you're 6 saying there is a need for treatment before the 7 mutation is identified as amenable, is that 8 fair? 9 A. No. What I am saying, there is the 10 need for treatment, and I need to define what 11 the best treatment strategy is. And by 12 understanding the mutation status has helped me 13 define what the treatment strategy is to be 14 pursued. 15 Q. So would a mutation that was 16 amenable to migalastat though, would the need 17 for migalastat arise before the mutation was 18 actually identified as amenable? 19 A. I'm sorry, maybe I'm not 20 understanding your logic there. So please 21 rephrase or ask that again. I apologize. 22 Q. Sure. 23 So would the need for migalastat for 24 a mutation that we now know is amenable, would 25 the need for migalastat have arisen for that</p>

18 [REDACTED]
19 [REDACTED] et
20 me rephrase that.
21 How is migalastat amenability
22 determined?
23 A. Yeah, it's typically determined
24 through use of an assay to look for amenability.
25 [REDACTED]

18 [REDACTED]
19 [REDACTED]
20 [REDACTED]
21 [REDACTED]
22 [REDACTED]
23 [REDACTED]
24 Q. But if you had referred to the
25 migalastat assay prior to May 2017, you would

Conducted on June 26, 2025

<p>101</p> <p>1 have been referring to the R&D HEK assay?</p> <p>2 A. Yes, sir, that is correct. That is</p> <p>3 correct.</p> <p>4 Q. And so what is your understanding of</p> <p>5 the differences between the R&D HEK assay and</p> <p>6 the GLP HEK assay?</p> <p>7 A. As I said, sir, I don't really have</p> <p>8 enough knowledge and it's not my field of</p> <p>9 expertise to define the differences between the</p> <p>10 two. But I'm sure that that's readily available</p> <p>11 somewhere in the literature in R&D or something,</p> <p>12 so...</p> <p>13 Q. Have you ever run a HEK assay to</p> <p>14 determine migalastat amenability?</p> <p>15 A. Personally, I have never ran a HEK</p> <p>16 assay.</p> <p>17 [REDACTED]</p> <p>18 [REDACTED]</p> <p>19 [REDACTED]</p> <p>20 [REDACTED]</p> <p>21 [REDACTED]</p> <p>22 [REDACTED]</p> <p>23 [REDACTED]</p> <p>24 [REDACTED]</p> <p>25 [REDACTED]</p>	<p>103</p> <p>1 a few minutes ago. I think that's what a</p> <p>2 relatively layman's explanation of what I</p> <p>3 meant -- or maybe more than a layman, but a very</p> <p>4 general knowledge of what an assay is.</p> <p>5 Q. And do you have an understanding as</p> <p>6 to the changes that Amicus made to the R&D HEK</p> <p>7 assay in order to arrive at the current assay?</p> <p>8 A. I am not aware, sir.</p> <p>9 Q. Just to button this up, do you</p> <p>10 consider yourself qualified to testify in court</p> <p>11 regarding the details of the HEK assays?</p> <p>12 A. Regarding the HEK assays? No, I do</p> <p>13 not.</p> <p>14 Q. Do you consider yourself qualified</p> <p>15 to testify in court regarding the differences</p> <p>16 between different HEK assays?</p> <p>17 A. No, sir.</p> <p>18 Q. Do you consider yourself qualified</p> <p>19 to testify regarding the superiority of one HEK</p> <p>20 assay over another?</p> <p>21 A. No, sir.</p> <p>22 Q. Do you consider yourself qualified</p> <p>23 to testify regarding a person of ordinary skill</p> <p>24 in the art's knowledge or understanding of HEK</p> <p>25 assays prior to May 2017?</p>
<p>102</p> <p>1 [REDACTED]</p> <p>2 [REDACTED]</p> <p>3 [REDACTED]</p> <p>4 [REDACTED]</p> <p>5 [REDACTED]</p> <p>6 [REDACTED]</p> <p>7 [REDACTED]</p> <p>8 [REDACTED]</p> <p>9 [REDACTED]</p> <p>10 [REDACTED]</p> <p>11 [REDACTED]</p> <p>12 [REDACTED]</p> <p>13 [REDACTED]</p> <p>14 [REDACTED]</p> <p>15 [REDACTED]</p> <p>16 [REDACTED]</p> <p>17 [REDACTED]</p> <p>18 [REDACTED]</p> <p>19 [REDACTED]</p> <p>20 Q. So I take it if I asked you to</p> <p>21 explain to me the details of either of the</p> <p>22 assays we have been just talking about, that you</p> <p>23 would not be able to do so, is that right?</p> <p>24 A. Not to any sophisticated degree, I</p> <p>25 mean, more than just what I talked to you about</p>	<p>104</p> <p>1 A. No, sir.</p> <p>2 Q. Do you consider yourself qualified</p> <p>3 to testify regarding a person of ordinary skill</p> <p>4 in the art's knowledge or understanding of HEK</p> <p>5 assays prior to August 2019?</p> <p>6 A. No, sir.</p> <p>7 Q. Do you consider yourself qualified</p> <p>8 to testify regarding the accuracy of any HEK</p> <p>9 assay in determining migalastat amenability?</p> <p>10 A. No, sir.</p> <p>11 Q. Was there a long-felt but unmet need</p> <p>12 for mutations identified as migalastat amenable</p> <p>13 using the R&D HEK assay prior to 2017?</p> <p>14 A. Was there an unmet need related to</p> <p>15 the assay? I wouldn't think so per se. I think</p> <p>16 it was -- it would be more related to the</p> <p>17 mutations themselves, not necessarily the assay.</p> <p>18 Q. So I'm going to ask a similar</p> <p>19 question but focusing on the newer assay, the</p> <p>20 current assay.</p> <p>21 A. Yes, sir.</p> <p>22 Q. So was there a long-felt but unmet</p> <p>23 need for mutations identified as amenable using</p> <p>24 the GLP HEK assay?</p> <p>25 A. There is a long-felt unmet need</p>

AMICUS'S OPPOSITION TO AUROBINDO'S MOTION *IN LIMINE* NO. 1

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AMICUS THERAPEUTICS US, LLC and
AMICUS THERAPEUTICS, INC.,

Plaintiffs,

v.

TEVA PHARMACEUTICALS USA, INC.
and TEVA PHARMACEUTICALS, INC.,

Defendants.

C.A. No. 22-1461 (CJB)
(Consolidated)

Exhibit 18

**AMICUS'S OPPOSITION TO AUROBINDO'S MOTION *IN LIMINE* NO. 1 TO
PRECLUDE PLAINTIFFS' EXPERT TESTIMONY REGARDING THE HEK ASSAY**

Aurobindo's motion should be denied because Amicus's experts Dr. Hopkin and Dr. Jefferies are testifying on issues within the scope of their expert reports, including their discussions of the relevant HEK assays, all of which they are qualified to offer. Each of Dr. Hopkin and Dr. Jefferies is a practicing clinician with significant experience treating Fabry patients who have HEK assay amenable mutations with Galafold, and they have submitted expert reports, based on their own medical experiences as well as the scientific literature, that apply their significant experience and understanding of the scientific literature to the facts of this case. *See, e.g.*, Ex. A, ¶¶ 1-21, Ex. 1; Ex. B, ¶¶ 1-18, Ex. 1; Ex. C, ¶ 2. Specifically, as they testified at deposition, Dr. Hopkin and Dr. Jefferies each know what a HEK assay is and does and how it relates to the facts of this case. *See, e.g.*, Mot., Ex. A at 67:23-68:1 ("Q. What is a HEK assay? A. It is a method for assessing the response – in this case, the response of the cells to migalastat."); *id.*, Ex. B at 98:21-24 ("Q. How is migalastat amenability determined? A. Yeah, it is typically determined through the use of an assay to look for amenability."). Further, Dr. Jefferies testified that he was aware there were differences between the HEK assay used in Amicus's clinical trials and the later migalastat amenability assay. *Id.* at 99:17-100:23.

As an initial matter, Aurobindo's motion should be denied because it is an improper *Daubert* motion styled as a motion *in limine*, challenging the qualifications of Amicus's experts. *See, e.g., Biogen Inc. v. Sandoz Inc.*, C.A. No. 22-1190-GBW, 2025 WL 1260954, at *8-9 (D. Del. May 1, 2025). But to the extent this motion is considered, Amicus's experts' opinions are proper under Federal Rule of Evidence 702, which provides that Amicus's experts may testify on that subject matter where, as here,

it is more likely than not that: (a) the expert's scientific, technical, or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue; (b) the testimony is based on sufficient facts or data; (c) the testimony is the product of reliable principles and methods; and (d) the expert's

opinion reflects a reliable application of the principles and methods to the facts of the case.

Aurobindo's motion fails because, as Aurobindo admits, the asserted claims in this case are method of treatment claims and are not directed to designing or running the HEK assay itself. Mot. at 1. Notably, having experience designing or running a HEK assay is not required under either party's definition of a person of ordinary skill in the art ("POSA"). See Ex. D (Opening Expert Report of Jeffery Medin, Ph.D.), ¶ 30; Ex. B (Rebuttal Expert Report of Robert Hopkin, M.D.), ¶ 29. Specifically, the parties' POSA definitions are as follows:

Aurobindo's definition: [T]hose familiar with the field of metabolic disorders such as Fabry disease and would include pharmaceutical chemists or physicians involved in research and development of formulations for treatment of such disorders, who would have a Master's, Ph.D., and/or M.D. degree and several years of experience in the field (Ex. D, ¶ 30); and

Amicus's definition: An individual with a degree in biology, pharmacology, medicine, or a related discipline with one to two years of experience in Fabry disease. (Ex. B, ¶ 29).

Accordingly, Drs. Hopkin and Jefferies are each a POSA, and Aurobindo does not argue otherwise in its motion.

Amicus would be severely prejudiced if Aurobindo's motion were granted, and such prejudice would be difficult if not impossible to cure now that the parties are weeks from trial. In contrast, Aurobindo does not allege any prejudice from denial of this motion because there is none. See generally Mot. at 1-3. To the extent that Aurobindo alleges that the testimony of Amicus's experts is not reliable, Aurobindo can cross-examine Amicus's experts on the HEK assay at trial. And courts deny motions to exclude expert opinions where, as here, Aurobindo's complaints go to the weight the Court should accord their testimony which can be tested through cross-examination at trial. See, e.g., *Leonard v. Stemtech Health Scis., Inc.*, 981 F. Supp. 2d 273, 280-81 (D. Del. 2013) (denying motion because expert's knowledge of use of an electron

scanning microscope was “at least greater than that of the average layman” even though the expert “has never used an electron microscope himself”); *S. Track & Pump, Inc. v. Terex Corp.*, 852 F. Supp. 2d 456, 469 (D. Del. 2012) (“[A]ny alleged shortcomings or deficiencies in [expert’s] opinions are issues of weight and credibility appropriately addressed through cross-examination”); *Inline Connection Corp. v. AOL Time Warner Inc.*, 472 F. Supp. 2d 604, 613 (D. Del. 2007) (same).

Amicus is further concerned that Aurobindo’s motion is a backdoor attempt to exclude all of Dr. Hopkin’s and Dr. Jefferies’ validity opinions as to the asserted claims. Aurobindo fails to identify what portions or paragraphs of Dr. Hopkin’s or Dr. Jefferies’ expert reports it seeks to exclude through its motion other than saying that its motion is directed to their testimony “regarding the HEK Assay.” Mot. at 2. But the words “HEK assay amenable mutation” appears in the asserted claims. *See, e.g.*, Ex. E, Cls. 8 & 36. Surely, Amicus’s experts are permitted to testify as to that subject matter which is within the scope of their expert reports. Next, Aurobindo selectively quotes from the deposition transcripts of Drs. Hopkin and Jefferies as a basis to preclude their testimony. But none of those quotes is the admission Aurobindo claims them to be. *See, e.g.*, Mot., Ex. A at 68:22-70:3 (testimony Aurobindo does not cite where Dr. Hopkin describes changes made to the HEK assay); *id.*, Ex. B at 100:5-23 (testimony Aurobindo does not cite where Dr. Jefferies explains that the later HEK assay “has been refined” since the R&D assay); *see also* Mot. at 1-2.

Accordingly, Aurobindo’s motion should be denied.

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August 11, 2025

EXHIBIT A

**THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE**

AMICUS THERAPEUTICS US, LLC and
AMICUS THERAPEUTICS, INC.,

Plaintiffs,

V.

TEVA PHARMACEUTICALS USA, INC.,
and TEVA PHARMACEUTICALS, INC.,

Defendants.

C.A. No. 22-1461 (CJB)
CONSOLIDATED

**CONFIDENTIAL – SUBJECT
TO PROTECTIVE ORDER**

OPENING REPORT OF JOHN L. JEFFERIES, M.D.

April 4, 2025

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I. INTRODUCTION

1. I have been retained by Groombridge, Wu, Baughman & Stone LLP, counsel for Plaintiffs Amicus Therapeutics US, LLC and Amicus Therapeutics, Inc. (which I will refer to as “Amicus”) to provide expert testimony about certain objective indicia of non-obviousness regarding the patent claims I understand to have been asserted in this litigation. I have been informed that in this case Amicus contends Defendants Aurobindo Pharma Ltd. and Aurobindo Pharma USA, Inc. (which I will refer to as “Aurobindo”) infringe Claims 8 and 36 of the ’388 Patent, Claims 17 and 23 of the ’489 Patent, Claim 9 of the ’490 Patent, and Claims 23–27 of the ’164 Patent. Those are the only claims in the patents for which I have been asked to provide an opinion. I refer to all four patents together as the “Asserted Patents,” and all asserted claims together as the “Asserted Claims.” I refer to the ’388, ’489, and ’490 Patents as the “Reassessment Mutations Patents.” I refer to the ’164 Patent as the “Engineered Mutations Patent.”

2. Below, I provide my opinions about (1) the long-felt but unmet need for Amicus’s inventions claimed in the Asserted Claims of the Reassessment Mutations Patents (that is, Claims 8 and 36 of the ’388 Patent, Claims 17 and 23 of the ’489 Patent, and Claim 9 of the ’490 Patent) and the Engineered Mutations Patent (that is, Claims 23–27 of the ’164 Patent); (2) the failures of others to solve the problem solved by Amicus’s inventions claimed in the Asserted Claims of the Reassessment Mutations Patents (that is, Claims 8 and 36 of the ’388 Patent, Claims 17 and 23 of the ’489 Patent, and Claim 9 of the ’490 Patent); and (3) the industry praise for Amicus’s inventions claimed in the Asserted Claims of the Reassessment Mutations Patents (that is, Claims 8 and 36 of the ’388 Patent, Claims 17 and 23 of the ’489 Patent, and Claim 9 of the ’490 Patent).

3. I reserve the right to consider additional materials and to amend or supplement my opinions in light of additional information that may come to my attention, including any critique of my report or opinions advanced by or on behalf of Amicus.

4. I may rely on visual aids and demonstrative exhibits that demonstrate the bases of my opinions. Examples of these visual aids and demonstrative exhibits may include, for example, claim charts, patent drawings, excerpts from patent specifications, file histories, interrogatory responses, deposition testimony, and deposition exhibits, as well as physical exhibits, charts, photographs, diagrams, videos, and animated or computer-generated graphics.

II. SUMMARY OF OPINIONS

5. *First*, before the priority date of the Asserted Claims there was a long-felt but unmet need that supports the non-obviousness of the claims. Regarding the Reassessment Mutations Patents, it is my opinion that, before the priority date of the Asserted Claims of the Reassessment Mutations Patents, there was a long-felt but unmet need that supports the non-obviousness of the claims, namely for a better method of effectively treating Fabry patients with certain α -Gal A mutations:

- **Claim 8 of the '388 Patent:** A13P, A20D, Q57L, G80D, P146S, D175E, K213M, I242F, M267T, A309V, V316I, V316G, P323R, A352G, R356P, T385A, V390M, and G395A;
- **Claim 36 of the '388 Patent:** G80D, P146S, M267T, and R356P;
- **Claim 17 of the '489 Patent:** A13T, N34T, M42K, L54F, P60T, E87D, L89F, Y123C, H125L, I133M, K140T, F145S, P146R, Y152H, D165G, p.M187_S188dup, V199G, M208R, I219L, N224T, Q250R, G261C, G271D, M284V, I303F, D322N, G325R, K326N, G334E, E358Q, E358D, G361E, G375E, T412N, and M421V;
- **Claim 23 of the '489 Patent:** L54F, L89F, K140T, and G334E; and
- **Claim 9 of the '490 Patent:** I242F.

Regarding the Engineered Mutations Patent, before the priority date of the Asserted Claims of the Engineered Mutations Patent, there was a long-felt but unmet need that supports the non-obviousness of the claims, namely for a better method of effectively treating Fabry patients with certain α -Gal A mutations that were previously unknown to be associated with Fabry disease because any delay in treatment could be costly to the patient:

- **Claims 23 and 24 of the '164 Patent:** Y184S, N228H, and T412I;
- **Claim 25 of the '164 Patent:** Y184S;
- **Claim 26 of the '164 Patent:** N228H; and
- **Claim 27 of the '164 Patent:** T412I.

These long-felt but unmet needs were fulfilled by the inventions claimed in the Asserted Claims.

6. ***Second***, it is my opinion that, before the priority date of the Asserted Claims for the Reassessment Mutations Patents, failures of others support the non-obviousness of the claims, namely the failures to find a better (for example, non-enzyme replacement therapy (“ERT”)) method of effectively treating Fabry patients with certain α -Gal A mutations:

- **Claim 8 of the '388 Patent:** A13P, A20D, Q57L, G80D, P146S, D175E, K213M, I242F, M267T, A309V, V316I, V316G, P323R, A352G, R356P, T385A, V390M, and G395A;
- **Claim 36 of the '388 Patent:** G80D, P146S, M267T, and R356P;
- **Claim 17 of the '489 Patent:** A13T, N34T, M42K, L54F, P60T, E87D, L89F, Y123C, H125L, I133M, K140T, F145S, P146R, Y152H, D165G, p.M187_S188dup, V199G, M208R, I219L, N224T, Q250R, G261C, G271D, M284V, I303F, D322N, G325R, K326N, G334E, E358Q, E358D, G361E, G375E, T412N, and M421V;
- **Claim 23 of the '489 Patent:** L54F, L89F, K140T, and G334E; and
- **Claim 9 of the '490 Patent:** I242F.

7. ***Third***, it is my opinion that industry praise of GALAFOLD supports the non-obviousness of the Asserted Claims of the Reassessment Mutations Patents.

III. PROFESSIONAL BACKGROUND AND QUALIFICATIONS

8. I have extensive experience treating both children and adults with Fabry disease. I completed fellowships both in adult cardiology and pediatric cardiology and have focused much of my career on heritable cardiovascular disease. I have been responsible for the management of cardiovascular implications of patients with Fabry disease over the last 24 years. I have treated these patients with existing standard of care therapies including enzyme replacement therapy and chaperone therapy. In addition, I have been involved in clinical trials investigating therapeutic options in patients with Fabry disease. This has resulted in familiarity of the benefits and limitations of a variety of different therapeutic options for the disease. As seen in my curriculum vitae, I have delivered multiple lectures and co-authored numerous abstracts and manuscripts on the topic of Fabry disease.

9. I am a professor of Public Health at the University of Memphis School of Public Health, a research member at St. Jude Children's Research Hospital, and a professor of clinical cardiology at the Baptist Health Sciences University College of Osteopathic Medicine. I have held those positions since 2023, 2018, and 2023, respectively.

10. I received my M.D. from the University of Tennessee College of Medicine and then served as a resident in internal medicine and pediatrics at the University of Kentucky. I was also a fellow in general internal medicine at the University of Kentucky and completed fellowships in adult cardiovascular diseases, pediatric cardiology, and pediatric cardiac transplantation at the Texas Heart Institute, St. Luke's Episcopal Hospital, and Texas Children's Hospital at Baylor College of Medicine.

11. In 2001, I received a Master of Public Health with a major in epidemiology from the University of Kentucky. In 2023, I received a Master of Business Administration with

majors in management, entrepreneurship, and innovation from the Wharton School of Business at the University of Pennsylvania.

12. I have held academic positions at several well-known institutions. From 2006 to 2010, I served as an assistant professor in medicine and adult cardiovascular diseases at Baylor College of Medicine. From 2008 to 2010, I was an assistant professor in adult cardiovascular diseases and pediatric cardiology at the M.D. Anderson Cancer Center at University of Texas. From 2010 to 2015, I was associate professor in medicine and adult cardiovascular diseases at University of Cincinnati and an associate professor in pediatric cardiology at Cincinnati Children's Hospital Medical Center. From 2015 to 2018, I was a professor of adult cardiovascular diseases at the University of Cincinnati and a professor in pediatric cardiology as well as the division of human genetics at Cincinnati Children's Hospital Medical Center. From 2018 to 2023, I was a tenured professor of adult cardiovascular diseases and preventive medicine at the University of Tennessee, chair of the Methodist Cardiovascular Institute in Adult Cardiovascular Diseases, and a professor in pediatric cardiology at Le Bonheur Children's Hospital. In 2018, I became a research member in adult and pediatric cardiology at St. Jude Children's Research Hospital. In 2023, I accepted a position at the University of Memphis as a professor in the School of Public Health's Cardiovascular Outcomes Center.

13. Since 2001, I have presented more than 300 talks and have published more than 300 book chapters and manuscripts in prestigious journals such as *Circulation*, *Circulation Research*, *JAMA*, *JAMA Cardiology*, *Lancet*, *Lancet Oncology*, *Lancet Neurology*, and *The New England Journal of Medicine*. Many of these publications are related to the genetic underpinnings of cardiovascular disease, innovative approaches to heart failure therapy, artificial

intelligence, and cardiovascular implications of heritable disorders like Fabry disease.¹ I have been the principal investigator for multiple Research Project and Cooperative Agreement grants from the National Institutes of Health.

14. I have also published several important studies related to Fabry disease research, particularly concerning the management and treatment of children with Fabry disease. I contributed to the development of consensus guidelines for the management and treatment of children with Fabry disease. These guidelines emphasize early diagnosis, proactive monitoring, and individualized treatment plans to optimize outcomes in young patients with Fabry disease. I have also published on identifying patients at elevated risk for Fabry disease using machine learning.

15. Outside of academia, I have been involved with several biotechnology and pharmaceutical companies. From 2023 to 2024, I served as Director of Medical Affairs, Cardiovascular at Bristol Myers Squibb. Since 2022, I have served as Chief Medical Officer at Daxor Corporation, which focuses on blood volume testing innovation. Since 2023, I have served as Chief Medical Officer at Nuwellis, which is a medical technology company that develops therapies for fluid overload.

16. I have received numerous prestigious awards throughout my career that recognize excellence in pediatrics, cardiology, research, and teaching. Early in my training, I was honored

¹ See, e.g., Towbin, J., Jefferies, J., (2017) Cardiomyopathies Due to Left Ventricular Noncompaction, Mitochondrial & Storage Diseases, & Inborn Errors of Metabolism, *Circulation Rsch.* **121**:838 (ATGAL_10161588); Wessel, D. *et al.*, (2013) Clopidogrel in Infants with Systemic-to-Pulmonary-Artery Shunts, *N. Engl. J. of Med.* **368**:2377 (ATGAL_10161618); Towbin, J. *et al.*, (2015) Left Ventricular Non-Compaction Cardiomyopathy, *Lancet* **386**:813 (ATGAL_10161605); Hopkin, R.J. *et al.*, (2015) The Management & Treatment of Children with Fabry Disease: A United States-Based Perspective, *Mol. Genet. Metab.* **117**:104 (ATGAL_09536787).

with multiple Outstanding Resident Awards in pediatric cardiology, intensive care, and nephrology, as well as the Outstanding Resident Research and Outstanding Teacher Awards at the University of Kentucky. My research contributions earned nominations and awards, including the Young Investigator Award Nominee, American Academy of Pediatrics Travel Grant, and Runner-Up Young Investigator Award for Clinical Research. I also received competitive grants and fellowships, such as the Bristol Myers Squibb American College of Cardiology Grant and the Thrasher New Researcher Award. Additionally, I was recognized for academic contributions with awards like the Outstanding Lecture Award from the Irish and American Pediatric Society and the American College of Cardiology Foundation (ACCF) Research Fellowship Award.

17. I have served as a peer reviewer for an extensive range of medical and scientific journals, contributing my expertise to over 80 journals across cardiology, pediatrics, genetics, and related fields. Since 2003, I have reviewed for prestigious publications such as *Circulation*, *Journal of the American College of Cardiology*, *Journal of Heart and Lung Transplantation*, *Pediatrics*, *Nature Communications*, *The Lancet Neurology*, and *European Journal of Paediatric Neurology*. I also serve on the Editorial Board of multiple international journals, such as the *Journal of the American Heart Association*.

18. I have served as a grant application reviewer for organizations, such as the Barth Syndrome Foundation and the Great Ormond Street Hospital Children's Charity, and serve on study sections for the American Heart Association's Cardiomyopathy Fellowship Peer Review Committee and the Strategically Focused Research Network (SFRN) Cardio-Oncology Basic Peer Review Committee. Additionally, I have held advisory roles on multiple boards, including the Korey Stringer Institute and The Dystrophic Epidermolysis Bullosa Research Association of

America, as well as Medtronic's Heart Failure Advisory Board. I continue to serve on the Barth Syndrome Foundation's International Scientific and Medical Advisory Board and recently joined the Harvard Business Review Advisory Council.

19. I am also the immediate past Governor of the Tennessee Chapter of the American College of Cardiology and immediate past President of the American Heart Association Mid-South region.

20. I am the team cardiologist for the Memphis Grizzlies professional basketball team, team cardiologist for the Memphis FC 901 professional soccer team, and team cardiologist for the Memphis Redbirds minor league baseball team.

21. My curriculum vitae is attached as **Exhibit 1**.

IV. COMPENSATION AND PRIOR TESTIMONY

22. I am being compensated at the rate of \$750 per hour, which is my standard rate. My rate is not contingent on the opinions set forth in this report or on the outcome of this litigation.

23. Within the past four years, I have not provided testimony as an expert at trial or by deposition.

V. DOCUMENTS AND MATERIALS REVIEWED

24. The opinions I express in this report are based on my own knowledge and experience, and also on documents I have received and considered, including scientific publications, which are cited or referenced within this report and/or listed in **Exhibit 2**.

VI. GENERAL LEGAL PRINCIPLES

25. I have been informed that a patent claim is presumed valid, and that a patent claim can be found invalid for obviousness based on evidence that the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would

have been obvious at the time of the invention to a person of ordinary skill in the art. I have not been asked to opine on whether any patent claims are valid.

26. What I have been asked to opine on is certain other factors that may be considered in assessing whether the invention is or is not obvious that are known as objective indicia or secondary considerations. The specific factors that I have been asked to consider for objective indicia include a long-felt but unmet need that was satisfied by the claimed invention; whether others tried but failed to solve the problem solved by the claimed invention; and whether there has been industry praise of the claimed invention.

27. I have been informed that evidence of a long-felt but unmet need can support the non-obviousness of an invention because if the invention were obvious someone else would have developed it sooner to satisfy that long-felt need. The relevant time period for determining whether there had been an unmet, persistent need is as of the priority date for the patent in question. I have also been informed that in order to show satisfaction of long-felt need, one must establish that (1) a person of ordinary skill recognized a problem that existed for a long period of time without a solution, (2) the long-felt need had not been satisfied by another before the claimed invention, and (3) the invention in fact satisfied the long-felt need.

28. I have been informed that evidence of each of these objective indicia is relevant to non-obviousness only if a nexus, i.e., a connection, exists between the evidence of the objective indicia and the product's characteristics that embody that claimed invention. Counsel for Amicus has also informed me that although the defendant bears the burden of proving obviousness by clear and convincing evidence in all respects, the patent owner bears a burden of production in demonstrating objective indicia, including nexus.

VII. THE INVENTIONS OF THE ASSERTED CLAIMS

29. The inventions of the Asserted Claims are methods of using migalastat to treat Fabry patients having the particular α -Gal A mutations listed in the Asserted Claims.

A. The Reassessment Mutations Patents

30. The Reassessment Mutations Patents share a common specification. I was informed by counsel that there is no dispute that the priority date of the Reassessment Mutations Patents is May 30, 2017.

31. The Asserted Claims of the Reassessment Mutations Patents disclose methods of treatment with migalastat to treat Fabry patients who have certain α -Gal A mutations.

1. Claims 8 and 36 of the '388 Patent

32. Claim 8 of the '388 Patent depends from claim 1. Claim 36 depends from claim 7, which depends from claim 1. The claim language is:

1. A method of treating Fabry disease, the method comprising administering migalastat to a patient in need thereof, wherein the patient has an α -galactosidase A protein comprising a HEK assay amenable mutation selected from the group consisting of: A13P, A20D, Q57L, G80D, P146S, D175E, K213R, K213M, I242F, M267T, A309V, V316I, V316G, P323R, A352G, R356P, T385A, V390M, and G395A.
7. The method of claim 1, wherein the mutation is selected from the group consisting of: G80D, P146S, M267T and R356P.
8. The method of claim 1, wherein the mutation is selected from the group consisting of: A13P, A20D, Q57L, G80D, P146S, D175E, K213M, I242F, M267T, A309V, V316I, V316G, P323R, A352G, R356P, T385A, V390M, and G395A.
36. The method of claim 7, wherein the patient is administered about 150 mg of migalastat hydrochloride every other day.

2. Claims 17 and 23 of the '489 Patent

33. Claim 17 of the '489 Patent depends from claim 11. Claim 23 depends from claim 22, which depends from claim 11. The claim language is:

11. A method of treating Fabry disease, the method comprising administering migalastat to a patient in need thereof, wherein the patient has an α -galactosidase A protein comprising a HEK assay amenable mutation selected from the group consisting of A13T, N34T, M42K, L54F, P60T, E87D, L89F, Y123C, H125L, I133M, K140T, F145S, P146R, Y152H, D165G, p.M187_S188dup, V199G, M208R, I219L, N224T, Q250R, G261C, G271D, M284V, I303F, D322N, G325R, K326N, G334E, E358Q, E358D, G361E, G375E, T412N and M421V.
17. The method of claim 11, wherein the patient is administered about 150 mg of migalastat hydrochloride every other day.
22. The method of claim 11, wherein the mutation is selected from the group consisting of: L54F, L89F, K140T and G334E.
23. The method of claim 22, wherein the patient is administered about 150 mg of migalastat hydrochloride every other day.

3. Claim 9 of the '490 Patent

34. Claim 9 of the '490 Patent depends from claim 7, which depends from claim 1.

The claim language is:

1. A method of treating Fabry disease, the method comprising administering migalastat to a patient in need thereof, wherein the patient has an α -galactosidase A protein comprising a HEK assay amenable mutation selected from the group consisting of: I242F, G334E, N34D and p.V254del.
7. The method of claim 1, wherein the patient is administered about 150 mg of migalastat hydrochloride every other day.
9. The method of claim 7, wherein the mutation is I242F.

B. The Engineered Mutations Patent

35. I was informed by counsel that there is no dispute that the priority date of the Engineered Mutations Patent is August 7, 2019.

36. The Asserted Claims of the Engineered Mutations Patent disclose methods of treatment with migalastat to treat Fabry patients who have one of the following α -Gal A mutations: Y184S, N228H, and T412I. The claims further disclose orally administering to the

patient about 123mg free base equivalent of migalastat or a salt thereof (e.g., 150mg of migalastat hydrochloride salt) every other day.

1. Claims 23–27 of the '164 Patent

37. The claim language of claims 23–27 of the '164 Patent is as follows:

23. A method for treatment of Fabry disease in a human patient in need thereof, the method comprising orally administering to the patient about 123 mg free base equivalent of migalastat or a salt thereof every other day, wherein the patient has an α -galactosidase A mutation selected from the group consisting of: Y184S, N228H, or T412I.

24. The method of claim 23, wherein the patient is administered about 150 mg of migalastat hydrochloride every other day.

25. The method of claim 23, wherein the patient has the mutation Y184S.

26. The method of claim 23, wherein the patient has the mutation N228H.

27. The method of claim 23, wherein the patient has the mutation T412I.

C. Table of Claimed Mutations

	Mutation	Asserted Claim(s) (bolded mutations and claims are in the Engineered Mutations Patent)
1	A13P	'388 Patent, Claim 8
2	A13T	'489 Patent, Claim 17
3	A20D	'388 Patent, Claim 8
4	N34T	'489 Patent, Claim 17
5	M42K	'489 Patent, Claim 17
6	L54F	'489 Patent, Claim 17; '489 Patent, Claim 23
7	Q57L	'388 Patent, Claim 8
8	P60T	'489 Patent, Claim 17
9	G80D	'388 Patent, Claim 8; '388 Patent, Claim 36
10	E87D	'489 Patent, Claim 17
11	L89F	'489 Patent, Claim 17; '489 Patent, Claim 23
12	Y123C	'489 Patent, Claim 17
13	H125L	'489 Patent, Claim 17
14	I133M	'489 Patent, Claim 17
15	K140T	'489 Patent, Claim 17; '489 Patent, Claim 23
16	F145S	'489 Patent, Claim 17
17	P146R	'489 Patent, Claim 17

	Mutation	Asserted Claim(s) (bolded mutations and claims are in the Engineered Mutations Patent)
18	P146S	'388 Patent, Claim 8; '388 Patent, Claim 36
19	Y152H	'489 Patent, Claim 17
20	D165G	'489 Patent, Claim 17
21	D175E	'388 Patent, Claim 8
22	Y184S	'164 Patent, Claims 23, 24, & 25
23	p.M187_S188dup	'489 Patent, Claim 17
24	V199G	'489 Patent, Claim 17
25	M208R	'489 Patent, Claim 17
26	K213M	'388 Patent, Claim 8
27	I219L	'489 Patent, Claim 17
28	N224T	'489 Patent, Claim 17
29	N228H	'164 Patent, Claims 23, 24, & 26
30	I242F	'388 Patent, Claim 8; '490 Patent, Claim 9
31	Q250R	'489 Patent, Claim 17
32	G261C	'489 Patent, Claim 17
33	M267T	'388 Patent, Claim 8; '388 Patent, Claim 36
34	G271D	'489 Patent, Claim 17
35	M284V	'489 Patent, Claim 17
36	I303F	'489 Patent, Claim 17
37	A309V	'388 Patent, Claim 8
38	V316I	'388 Patent, Claim 8
39	V316G	'388 Patent, Claim 8
40	D322N	'489 Patent, Claim 17
41	P323R	'388 Patent, Claim 8
42	G325R	'489 Patent, Claim 17
43	K326N	'489 Patent, Claim 17
44	G334E	'489 Patent, Claim 17; '489 Patent, Claim 23
45	A352G	'388 Patent, Claim 8
46	R356P	'388 Patent, Claim 8; '388 Patent, Claim 36
47	E358Q	'489 Patent, Claim 17
48	E358D	'489 Patent, Claim 17
49	G361E	'489 Patent, Claim 17
50	G375E	'489 Patent, Claim 17
51	T385A	'388 Patent, Claim 8
52	V390M	'388 Patent, Claim 8
53	G395A	'388 Patent, Claim 8
54	T412I	'164 Patent, Claims 23, 24, & 27
55	T412N	'489 Patent, Claim 17
56	M421V	'489 Patent, Claim 17

VIII. CLAIM CONSTRUCTION

38. I have been informed that the parties have agreed on the meaning of the claim term “**HEK assay amenable mutation**,” which appears in the Asserted Claims of the Reassessment Mutations Patents, specifically (1) claim 1 of the ’388 Patent from which asserted claims 8 and 36 depend, (2) claim 11 of the ’489 Patent from which asserted claims 17 and 23 depend, and (3) claim 1 of the ’490 Patent from which asserted claim 9 depends. I have been informed that the agreed-upon meaning is “mutant forms of α -galactosidase A (α -Gal A’) showing a relative increase of ≥ 1.2 -fold over baseline and an absolute increase of $\geq 3.0\%$ wild-type α -Gal A activity in the presence of 10 $\mu\text{mol/l}$ migalastat determined using the Good Laboratory Practice (‘GLP’)-validated HEK assay.” In forming my opinions, I have applied this construction to the Asserted Claims of the Reassessment Mutations Patents.

39. For all other claim terms, I have applied their plain and ordinary meaning.

IX. THE LEVEL OF ORDINARY SKILL IN THE ART

40. I have been informed that the claims are assessed from the standpoint of a person of ordinary skill in the art at the time of the invention. I have been informed that the relevant time frame for assessing the Reassessment Mutations Patents (’388, ’489, and ’490 Patents) is the priority date, May 30, 2017; and that the relevant time frame for assessing the Engineered Mutations Patent (’164 Patent) is the priority date, August 7, 2019.

41. In providing my opinion I have been asked to assume that the person of ordinary skill for the Reassessment Mutations and the Engineered Mutations Patents is:

An individual with a degree in biology, pharmacology, medicine, or a related discipline with one to two years of experience in Fabry disease. Such a person of ordinary skill may also work as part of a multi-disciplinary team and draw upon not only his or her own skills but also take advantage of certain specialized skills of others on the team to solve a given problem.

42. Based on my background and professional experience, by 2017 (for the Reassessment Mutations Patents) and by 2019 (for the Engineered Mutations Patent), I was a person of at least ordinary skill.

43. I understand that Aurobindo has offered the following alternative definition of the person of ordinary skill²:

Such skilled artisans would be those familiar with the field of metabolic disorders such as Fabry disease and would include pharmaceutical chemists or physicians involved in research and development of formulations for treatment of such disorders, who would have a Master's, Ph.D., and/or M.D. degree and several years of experience in the field. The amount of experience in the field would depend upon the level of formal education and particular experience with drugs for the treatment of Fabry disease. A POSA [person of ordinary skill in the art] would have worked in conjunction with other individuals, the group of which collectively would have had experience in these fields, as well as in the field of clinical development of drugs for the treatment of Fabry disease patients having renal impairment. A POSA would also have knowledge of the scientific literature concerning these fields as of the claimed priority date of the '388 (and '334) patent(s). A POSA may also work as part of a multidisciplinary team and draw upon not only his or her own skills but also take advantage of certain specialized skills of others in the team to solve a given problem.

Even under the definition of a person of ordinary skill proposed by Aurobindo, my opinions remain the same.

X. INTRODUCTION TO FABRY DISEASE AND GALAFOLD

A. Fabry Disease

44. Each cell in the body contains specialized organelles to perform particular functions necessary to the cell's survival.³ For example, certain proteins like secreted or membrane-bound proteins are synthesized in an organelle called the endoplasmic reticulum

² Aurobindo's Feb. 27, 2025 Suppl. Invalidity Contentions at 34–35.

³ See, e.g., Germain, D., (2010) Fabry Disease, *Orphanet J. of Rare Dis.* **5**:30 (ATGAL_10034456 at -456–57).

while certain old proteins and waste from the cell are broken down in an organelle called the lysosome.⁴ Lysosomes contain specific enzymes to break down and recycle waste fats, proteins, and other substances.⁵ Lysosomal storage diseases and disorders (“LSDs”) are metabolic diseases and disorders that are caused by enzyme deficiencies in the lysosome that result in buildups of those unwanted waste substances in cells.⁶ Accumulation of these substances in the body can damage cells and organs.⁷ Fabry disease is an inherited and rare LSD caused by mutations in the *GLA* gene, leading to either complete or partial deficiency of an enzyme called alpha-galactosidase A (α -Gal A).⁸ α -Gal A breaks down various substances, or substrates, including a fatty substance called globotriaosylceramide (sometimes abbreviated GL-3 or Gb3) and its derivatives such as globotriasosylsphingosine (lysoGb3).⁹ When the activity of α -Gal A is absent or diminished, its substrates such as GL-3 and lysoGb3 build up in the cells throughout the body, particularly cells lining blood vessels in the skin and in cells of the kidneys, heart, and nervous system.¹⁰ As the abnormal storage of substrates such as GL-3 and lyso Gb3 increases

⁴ See, e.g., Gros, F., Muller, S., (2023) The Role of Lysosomes in Metabolic & Autoimmune Diseases, *Nature Revs. Nephrology* **19**:366–83 (ATGAL_10161508 at -509–10).

⁵ See Sun, A., (2018) Lysosomal Storage Disease Overview, *Ann. Transl. Med.* **6**(24):476 (ATGAL_10161327 at -327); Gros, F., Muller, S., (2023) The Role of Lysosomes in Metabolic & Autoimmune Diseases, *Nature Revs. Nephrology* **19**:366–83 (ATGAL_10161508 at -509, -513, -521).

⁶ See Gros, F., Muller, S., (2023) The Role of Lysosomes in Metabolic & Autoimmune Diseases, *Nature Revs. Nephrology* **19**:366–383 (ATGAL_10161508 at -519–20).

⁷ E.g., *id.*

⁸ Germain, D., (2010) Fabry Disease, *Orphanet J. of Rare Dis.* **5**:30 (ATGAL_10034456 at -456–57, -476).

⁹ See *id.* at -456, -479.

¹⁰ *Id.* at -456–57.

over time, the cells are damaged and blood vessels in a patient become narrowed, leading to decreased blood flow and undernourishment of the tissues.¹¹

45. Fabry disease is referred to as an X-linked disorder because the *GLA* gene is found on the X chromosome.¹² Males have one X chromosome and one Y chromosome while females have two X chromosomes. This means that males with Fabry only have one copy of the *GLA* gene and thus a mutation in that copy can result in reduced or lost α -Gal A activity in all of the cells in the body.¹³ In females with Fabry disease, there are two copies of the *GLA* gene, one on each X chromosome although one copy is randomly inactivated.¹⁴ As such, depending on which copy is inactivated in a cell, in a majority of cases, the remaining copy is either the wild type form of the gene or the mutated form.¹⁵ Thus, approximately half the cells will have reduced to lost activity of α -Gal A while the other half have regular levels of α -Gal A activity.

46. Fabry disease is a progressive and systemic disease in both males and females. The average life expectancy for males with Fabry disease is around 58 years and it is around 75 years for females.¹⁶ In comparison, the average life expectancies for males and females without

¹¹ Desnick, R., Ioannou, Y., Eng, C., α -Galactosidase A Deficiency: Fabry Disease, *Online Metabolic & Molecular Bases of Inherited Disease* (McGraw-Hill Education; 2019), pp. 3733–44 (ATGAL_07011379 at -403).

¹² E.g., Izhar, R. *et al.*, (2023) Fabry Disease in Women: Genetic Basis, Available Biomarkers, & Clinical Manifestations, *Genes* **15**(1):37 (ATGAL_10161341 at -341–42).

¹³ *See id.* at -342, -353.

¹⁴ *See id.* at -342.

¹⁵ *See id.* at -342, -353.

¹⁶ Lidove, O. *et al.*, (2016) Fabry in the Older Patient: Clinical Consequences & Possibilities for Treatment, *Mol. Genet. Metab.* **118**(4):319 (ATGAL_00216964 at -964).

Fabry disease are 73.2 years and 79.1 years, respectively.¹⁷ Changes in the *GLA* gene that result in no α -Gal A activity cause the classical, severe form of Fabry disease whereas changes in the gene that result in diminished α -Gal A activity cause non-classical or late-onset Fabry disease.¹⁸ In classical Fabry disease, symptoms first appear during childhood or as teenagers in males, but later in females. In non-classical or late-onset Fabry disease, patients may have delayed manifestations and may have single-organ involvement.¹⁹

47. To date, more than 1,000 Fabry disease-associated mutations in the *GLA* gene have been identified.²⁰ Fabry disease associated mutations occur throughout the *GLA* gene and there appears to be no clear mutational hot spot.²¹ Moreover, various types of mutations have been identified, including point mutations (such as missense mutations, nonsense mutations, or mutations affecting splice sites), short-length rearrangement (generally considered rearrangements affecting less than 60 base pairs), and gross rearrangements (generally considered larger rearrangements that affect one or more exons).²² Approximately 60% of Fabry associated mutations are missense point mutations resulting in single amino acid substitutions in

¹⁷ Arias, E. *et al.*, (2022) Provisional Life Expectancy Estimates for 2021, *Nat'l Ctr. for Health Stat. Reps.* 23 (ATGAL_10161364 at -364).

¹⁸ Lidove, O. *et al.*, (2016) Fabry in the Older Patient: Clinical Consequences & Possibilities for Treatment, *Mol. Genet. Metab.* **118**(4):319 (ATGAL_00216964 at -964).

¹⁹ *Id.*

²⁰ Anania, M. *et al.*, (2025) Identification of Four New Mutations in the *GLA* Gene Associated with Anderson–Fabry Disease, *Int. J. Mol. Sci.* **26**(2):473 (ATGAL_10161380 at -386).

²¹ Gal, A., Schafer, E., Rohard, I., The Genetic Basis of Fabry Disease, *Fabry Disease: Perspectives from 5 Years of FOS* (NCBI Bookshelf; 2006) (ATGAL_00216171 at -171).

²² See Benjamin, E. *et al.*, (2017) The Validation of Pharmacogenetics for the Identification of Fabry Patients to be Treated with Migalastat, *Genet. Med.* **19**(4)436 (ATGAL_07871417 at -423).

α -Gal A enzyme.²³ The activity of each mutated α -Gal enzyme varies depending on the missense point mutation and may result in heterogenous phenotypes ranging from classical to non-classical Fabry disease.

48. Even though the affected α -Gal A enzyme leading to Fabry disease has been identified, reliable diagnosis of Fabry disease may be challenging.²⁴ Determining the amount of α -Gal A enzyme activity is a key diagnostic marker in males. In females, however, diagnosis is more difficult because of the X-linked nature of the disease; female patients can express normal residual activity in certain tissues, masking the deficiency in the enzymatic activity.²⁵ Further, patients with non-classical or late-onset Fabry disease may have single-organ involvement,²⁶ which can complicate diagnosis as classical organ involvements are missing in late-onset forms of the disease.²⁷ Recognition of Fabry disease is important because effective treatments are available, but they have to be prescribed early in the disease to be more effective in preventing organ damage.

49. Because the disease is progressive, untreated Fabry disease results in many severe health problems such as kidney failure, heart problems including enlargement of the left side of

²³ *Id.* at -417.

²⁴ Desnick, R., Ioannou, Y., Eng, C., α -Galactosidase A Deficiency: Fabry Disease, *Online Metabolic & Molecular Bases of Inherited Disease* (McGraw-Hill Ed. 2001), pp. 3733–44 (ATGAL_07011379 at -405).

²⁵ Wang, R. *et al.*, (2007) Heterozygous Fabry Women Are Not Just Carriers, But Have a Significant Burden of Disease & Impaired Quality of Life, *Genet. Med.* **9**(1):34–45 (ATGAL_08225720 at -720).

²⁶ Michaud, M. *et al.*, (2020) When & How to Diagnose Fabry Disease in Clinical Practice, *Am. J. Med. Scis.* **360**(6):641–49 (ATGAL_10161404 at -404).

²⁷ *Id.*

the heart and valve disease, gastrointestinal pain, neuropathic pain of the extremities, and cerebrovascular problems such as recurring stroke and vertigo.²⁸ Not every person with Fabry disease will have all the same symptoms of disease progression; however, the disease always gets worse over time and may lead to premature death if left untreated, making early diagnosis and treatment especially important for successful patient outcomes.²⁹

B. GALAFOLD and the Asserted Claims of Amicus's Patents

50. On December 14, 2017, Amicus filed a new drug application ("NDA") with the Food and Drug Administration ("FDA") requesting approval of migalastat for the treatment of patients 16 years and older with Fabry disease who have amenable mutations.³⁰ The NDA submission was based on clinical data, including reduction in disease-causing substrate (e.g., GL-3), from Amicus's clinical studies, including two Phase 3 pivotal studies in treatment-naïve patients (i.e., 011 Study, or FACETS) and ERT switch patients (i.e., 012 Study, or ATTRACT).³¹

51. On August 10, 2018, FDA approved GALAFOLD (migalastat) for the treatment of adults with a confirmed diagnosis of Fabry disease and a *GLA* mutation that was determined to be amenable to migalastat treatment using a specific in vitro amenability assay.³² FDA

²⁸ Dutra-Clarke, M. *et al.*, (2021) Variable Clinical Features of Patients with Fabry Disease & Outcome of Enzyme Replacement Therapy, *Mol. Genet. Metab. Reps.* **26**:100700 (ATGAL_10161393 at -393, -395).

²⁹ E.g., Patient Stories, FSIG, <https://fabry.org/patientstories/> (ATGAL_10161465 at -467–68).

³⁰ Dec. 14, 2017 Amicus Announcement, Amicus Therapeutics Submits New Drug Application to U.S. FDA for Migalastat for Treatment of Fabry Disease (ATGAL_05355923 at -923).

³¹ *Id.*

³² Aug. 10, 2018 FDA News Release, FDA Approves New Treatment for a Rare Genetic Disorder, Fabry Disease (ATGAL_09880475 at -475).

approved GALAFOLD under the accelerated approval pathway under which “FDA may approve drugs for serious conditions where there is an unmet medical need and where a drug is shown to have certain effects that are reasonably likely to predict a clinical benefit in patients.”³³ The GALAFOLD product insert, also known as the “label” or “prescribing information,” currently lists 367 *GLA* mutations as being amenable for treatment with GALAFOLD.³⁴

52. Migalastat, or 1,5-dideoxy-1,5-iminogalactitol, is a low molecular weight iminosugar. This iminosugar analog can be found in certain bacteria but is not naturally produced by humans.³⁵ Migalastat binds to the active site of the α -Gal A enzyme.³⁶ At high concentrations, migalastat can act as an inhibitor of α -Gal A enzyme activity.³⁷ At lower concentrations, migalastat can act as a pharmacological chaperone for α -Gal A.³⁸ The term “chaperone” refers to a broad class of molecules that influence the folding, structure, and/or stability of proteins. Chaperones vary in terms of structure, function, and specificity. Some proteins may act as chaperones while other chaperones are small molecules. Chaperones may

³³ Aug. 10, 2018 FDA News Release, FDA Approves New Treatment for a Rare Genetic Disorder, Fabry Disease (ATGAL_09880475 at -476).

³⁴ June 2024 GALAFOLD Prescribing Information, Table 2 (ATGAL_06388594 at -602–13).

³⁵ Lee, H. *et al.*, (2024) 1-Deoxynojirimycin-producing bacteria: production, optimization, biosynthesis, biological activities, *Biotech. & Bioproc. Eng'g* **29**(6):981–992 (ATGAL_10161496).

³⁶ McCafferty, E., Scott, L., (2019) Migalastat: A Review in Fabry Disease, *Drugs* **79**(5):543–54 (ATGAL_10161438 at -438).

³⁷ Pieroni, M. *et al.*, (2021) Cardiac Involvement in Fabry Disease, *J. Am. Coll. Cardiology* **77**(7):922–36 (ATGAL_10036328 at -337).

³⁸ *See id.*

also have broad activity or be specific to only one target. Chaperones that are specific to only a single protein, such as migalastat, are often referred to as “pharmacological chaperones.”³⁹

53. Migalastat’s mechanism of action in treating Fabry disease is due to its ability to reversibly bind to α -Gal A in the cell’s endoplasmic reticulum (sometimes referred to as the “ER”), stabilizing the α -Gal A so that it is not degraded in the ER and allowing it to be transported into the lysosome.⁴⁰ In the lysosome, α -Gal A is released from migalastat allowing the enzyme to break down its substrates such as GL-3 and lyso Gb3, including the accumulated GL-3 and lyso Gb3 caused by Fabry disease.⁴¹ Unfortunately, migalastat does not work with all *GLA* mutations that cause Fabry disease.⁴² Some mutations of *GLA* result in a loss of function where either no protein is created or the protein that is created has no enzymatic activity. Other mutations of *GLA* are thought to result in abnormally folded and less stable forms of α -Gal A that nevertheless retain some enzymatic activity. Only certain *GLA* mutations result in α -Gal A enzymes that retain enzymatic activity and can be stabilized by migalastat such that they can be transported into the lysosome. The GALAFOLD label provides that certain *GLA* mutations that were shown to have increased activity in a specified in vitro assay were deemed to be amenable to migalastat treatment. A list of amenable *GLA* mutations is provided in Table 2 of the product label.

³⁹ Liguori, L. *et al.*, (2020) Pharmacological Chaperones: A Therapeutic Approach for Diseases Caused by Destabilizing Missense Mutations, *Int. J. Mol. Sci.* **21**(2):489 (ATGAL_04808173 at -173).

⁴⁰ McCafferty, E., Scott, L., (2019) Migalastat: A Review in Fabry Disease, *Drugs* **79**(5):543–54 (ATGAL_10161438 at -438).

⁴¹ *Id.*

⁴² *Id.*

54. The mutations identified in the methods of treatment of the Asserted Claims are listed as amenable mutations to migalastat treatment in GALAFOLD's current label⁴³:

- **Claim 8 of the '388 Patent:** A13P, A20D, Q57L, G80D, P146S, D175E, K213M, I242F, M267T, A309V, V316I, V316G, P323R, A352G, R356P, T385A, V390M, and G395A;
- **Claim 36 of the '388 Patent:** G80D, P146S, M267T, and R356P;
- **Claim 17 of the '489 Patent:** A13T, N34T, M42K, L54F, P60T, E87D, L89F, Y123C, H125L, I133M, K140T, F145S, P146R, Y152H, D165G, p.M187_S188dup, V199G, M208R, I219L, N224T, Q250R, G261C, G271D, M284V, I303F, D322N, G325R, K326N, G334E, E358D, E358Q, G361E, G375E, T412N, and M421V;
- **Claim 23 of the '489 Patent:** L54F, L89F, K140T, and G334E;
- **Claim 9 of the '490 Patent:** I242F; and
- **Claims 23–27 of the '164 Patent:** Y184S, N228H, and T412I.

XI. OBJECTIVE INDICIA SUPPORTING NON-OBVIOUSNESS OF THE ASSERTED CLAIMS

A. Long-Felt But Unmet Need

55. For the reasons discussed below, treatment of Fabry disease with GALAFOLD fulfilled a long-felt but unmet need for an improved treatment for Fabry patients with amenable mutations to migalastat, including the claimed mutations. GALAFOLD is the first and only FDA-approved oral medication for the treatment of Fabry disease. Prior to the approval of GALAFOLD in 2018, Fabry patients in the U.S. would have had access only to ERT, i.e., agalsidase beta (FABRYZYME), which was approved by the FDA in April 2003.⁴⁴

⁴³ June 2024 GALAFOLD Prescribing Information, Table 2 (ATGAL_06388594 at -602–13).

⁴⁴ See, e.g., May 2010 FABRYZYME Prescribing Information (ATGAL_09687616 at -616).

1. Treatment Options Prior to GALAFOLD Had Drawbacks

56. From 2003 until the approval of GALAFOLD in 2018, the only FDA approved treatment for Fabry was enzyme replacement therapy with agalsidase beta, which is a recombinant form of human α -Gal A.⁴⁵ The term “enzyme replacement therapy,” or ERT, refers to a treatment using an artificial or recombinant version of the enzyme produced by genetically engineered cells.⁴⁶

57. The purpose of ERT is to provide a functional version of the enzyme, which a person with Fabry disease does not effectively make on their own.⁴⁷ This is accomplished by infusing the recombinant enzyme into the vein of a Fabry patient every other week.⁴⁸ The recombinant enzyme is subsequently taken up by the cells and breaks down its substrates such as GL-3 and lyso Gb3, including the accumulated excess of those substrates and thereby improving cellular function.⁴⁹ This reduction of substrate build up can slow the progression of Fabry disease.⁵⁰

58. There are drawbacks associated with ERT that have caused companies and researchers to focus on identifying alternative treatments: (i) treatment with ERT is burdensome for both the patient and caretakers, (ii) the generation of antibodies against the recombinant

⁴⁵ See, e.g., *id.*; Aug. 10, 2018 FDA News Release, FDA Approves New Treatment for a Rare Genetic Disorder, Fabry Disease (ATGAL_09880475 at -475).

⁴⁶ Germain, D., (2010) Fabry Disease, *Orphanet J. of Rare Dis.* 5:30 (ATGAL_10034456 at -483).

⁴⁷ May 2010 FABRAZYME Prescribing Information (ATGAL_09687616 at -628).

⁴⁸ *Id.* at -616.

⁴⁹ *Id.* at -617, at -627–628.

⁵⁰ *Id.*

enzyme is common and leads to infusion reactions and diminished efficacy, and (iii) the inability of the artificial enzyme to cross the blood-brain barrier and poor uptake into certain cells limits the utility of ERT in some patients.⁵¹

59. **ERT is burdensome for both patients and caregivers.** ERT requires that the patient receives IV infusions every two weeks for as long as the patient remains on treatment.⁵² The duration of infusion ranges between 30 minutes and eight hours based on the patient's tolerance but generally averages between two and three hours.⁵³ Infusions are generally administered in a medical setting such as a hospital or infusion center although the option of home infusions is becoming more common. The time and travel required for bi-weekly infusions can place a substantial burden upon patients and their caregivers particularly for school age children and working parents. Infusion related reactions ("IRRs") such as chills, fever, drop in blood pressure, nausea, and fatigue are common and many patients must take medication prior to the infusion in order to manage or prevent IRRs.⁵⁴ A recent survey found that 53% of current ERT patients require premedication.⁵⁵ Among those taking premedication approximately 40% of them reported that it posed a moderate or significant inconvenience.⁵⁶

⁵¹ See, e.g., '388 Patent at col. 2:13–26; '490 Patent at col. 2:28–41; '489 Patent at col. 2:28–41; '164 Patent at col. 1:66–2:12.

⁵² May 2010 FABRAZYME Prescribing Information (ATGAL_09687616 at -616).

⁵³ See Berry, L. *et al.*, (2024) Patient-Reported Experience with Fabry Disease & Its Management in the Real-World Setting: Results from a Double-Blind, Cross-Sectional Survey of 280 Respondents, *Orphanet J. Rare Diseases* **19**:153 (ATGAL_10161416 at -423).

⁵⁴ See *id.* at -417, -423.

⁵⁵ *Id.* at -423.

⁵⁶ *Id.*

60.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED].⁵⁷

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

57

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

61. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]⁵⁸

62. In many patients, treatment with ERT, which involves the infusion of a recombinant enzyme, causes the patient's immune system to create anti-drug antibodies or ADAs.⁵⁹ Approximately 83% of patients taking FABRAZYME developed ADAs with 77% of patients generating ADAs that inhibited the activity of the recombinant enzyme when tested.⁶⁰

⁵⁸ [REDACTED]

⁵⁹ Berry, L. *et al.*, (2024) Patient-Reported Experience with Fabry Disease & Its Management in the Real-World Setting: Results from a Double-Blind, Cross-Sectional Survey of 280 Respondents, *Orphanet J. Rare Diseases* **19**:153 (ATGAL_10161416 at -417).

⁶⁰ July 2024 FABRAZYME Prescribing Information (ATGAL_10161430 at -432).

These inhibitory ADAs bind to and neutralize the recombinant enzyme in the patient's blood decreasing the efficacy of ERT. A 2016 study of 168 Fabry patients on ERT found that that 40 percent of male patients developed inhibitory antibodies resulting in significantly higher lysoGb3 levels in their blood, increased MSSI and Disease Severity Scoring System (DS3) values, and decreased eGFR (a measure of kidney function).⁶¹ Patients developing inhibitory ADAs also had increased risk for diarrhea, tinnitus, fatigue, and neuropathic pain.⁶²

63. Further, ERT results in inefficient distribution of the recombinant enzyme leading to the limited effectiveness of ERT. The majority of administered recombinant enzyme accumulates in the liver, whereas cells of the heart and kidney, two of the most severely affected cell types in Fabry disease, take up very limited amounts of recombinant enzyme.⁶³ Further, ERT does little to solve central nervous system (CNS) manifestations of the disease because large proteins like wild-type α -Gal A cannot cross the blood-brain barrier.⁶⁴

64. Certain cell types are resistant to clearance of substrates such as GL-3 by ERT. Certain types of renal cells including podocytes, distal tubular cells, and arteriolar smooth

⁶¹ See, e.g., Lenders, M. *et al.*, (2016) Serum-Medicated Inhibition of Enzyme Replacement Therapy in Fabry Disease, *J. Am. Soc. Nephrol.* **27**:256–64 (ATGAL_06866922 at -926–28).

⁶² *Id.* at -925–26.

⁶³ See, e.g., '388 Patent at col. 2:22–26; '489 Patent at col. 2:37–41; '490 Patent at col. 2:37–41; '164 Patent at col. 2:8–12; Azevedo, O. *et al.*, (2021) Fabry Disease Therapy: State-of-the-Art & Current Challenges, *Int. J. Mol. Sci.* **22**(1):206 (ATGAL_04885416 at -421).

⁶⁴ See, e.g., '388 Patent at col. 2:16–22; '489 Patent at col. 2:31–37; '490 Patent at col. 2:31–37; '164 Patent at col. 2:2–8; Azevedo, O. *et al.*, (2021) Fabry Disease Therapy: State-of-the-Art & Current Challenges, *Int. J. Mol. Sci.* **22**(1):206 (ATGAL_04885416 at -421–22).

muscle cells are more resistant to clearance of substrates such as GL-3 and lyso Gb3 by ERT.⁶⁵ For example, one study (Mauer 2017) stated that glomerular podocytes are relatively resistant to clearance of GL-3 inclusions by ERT.⁶⁶ The study goes on to state that “[a]lthough a long-term ERT trial led to a reduced rate of renal, cardiac and cerebrovascular clinical events, there are substantial residual risks despite ERT. Thus, other treatment options are needed.”⁶⁷

2. GALAFOLD Addresses the Long Felt But Unmet Need for Better Methods of Treatment of Patients With Fabry Disease

65. It is my opinion that based on the drawbacks of Fabry disease treatments, there was an unmet medical need for the development of new less-burdensome therapies for Fabry disease. It is also my opinion that treatment of Fabry patients, including those with the claimed mutations, with GALAFOLD fulfilled that need, and therefore there is a nexus between the long-felt unmet need and the inventions claimed in the Asserted Claims of the Asserted Patents.

66. As I explained in Section X.B, GALAFOLD was approved under the accelerated approval pathway under which “FDA may approve drugs for serious conditions where there is an unmet medical need and where a drug is shown to have certain effects that are reasonably likely to predict a clinical benefit in patients.”⁶⁸ In its Multi-Discipline Review and Evaluation, FDA stated:

Despite approval of an ERT for FD, an unmet medical need exists for additional therapies. Confirmation that GL-3 inclusion reduction in kidney vasculature is

⁶⁵ Mauer, M. *et al.*, (2017) Reduction of Podocyte Globotriaosylceramide Content in Adult Male Patients with Fabry Disease with Amenable GLA Mutations Following 6 Months of Migalastat Treatment, *J. Med. Genet.* **54**:781 (ATGAL_06818690 at -690).

⁶⁶ *Id.*

⁶⁷ *Id.*

⁶⁸ Aug. 10, 2018 FDA News Release, FDA Approves New Treatment for a Rare Genetic Disorder, Fabry Disease (ATGAL_09880475 at -476).

associated with slower rate of progression of renal disease is still lacking. In addition, as any other ERT, agalsidase beta is associated with immune-mediated adverse reactions and the need for IV infusion of the product every 2 weeks for the duration of the patient's lifetime.⁶⁹

67. FDA recognized the potential in GALAFOLD as a viable option to fulfill unmet patient needs and granted accelerated approval of GALAFOLD for treatment of Fabry patients with a mutation that is amenable to migalastat based on in vitro amenability assay data, including the mutations of the Asserted Claims of the Reassessment Mutations Patents.

68. GALAFOLD addresses the drawbacks of ERT treatment for Fabry patients.

69. **First**, in contrast to ERT, GALAFOLD is an oral medication taken every other day, which results in higher patient compliance and a lower medical burden.⁷⁰ GALAFOLD provides "better quality of life and greater convenience of taking a 123-mg pill every two days, versus infusions every two weeks."⁷¹

70. **Second**, because GALAFOLD is not a recombinant enzyme, it does not trigger any immunogenicity response, does not suffer a loss of efficacy due to the generation of neutralizing ADAs, and is not associated with any infusion related reactions.⁷²

⁶⁹ Feb. 1, 2016 NDA Multi-Disciplinary Review and Evaluation for GALAFOLD (ATGAL_08244819 at -839).

⁷⁰ See, e.g., Moran, N., (2018) FDA Approves Galafold, a Triumph for Amicus, *Nat. Biotech.* **36**:91 (ATGAL_10161450 at -450); Müntze, J. *et al.*, (2023) Patient Reported Quality of Life & Medication Adherence in Fabry Disease Patients Treated with Migalastat: A Prospective, Multicenter Study, *Mol. Genet. Metab.* **138**(2):106981 (ATGAL_03972963).

⁷¹ Moran, N., (2018) FDA Approves Galafold, a Triumph for Amicus, *Nat. Biotech.* **36**:91 (ATGAL_10161450 at -450).

⁷² See, e.g., McCafferty, E., Scott, L., (2019) Migalastat: A Review in Fabry Disease, *Drugs* **79**(5):543–54 (ATGAL_10161438 at -446).

71. **Third**, as a small molecule, GALAFOLD also achieves broader tissue distribution and tissue penetration than the recombinant enzyme in ERT.⁷³ Studies suggest that migalastat readily diffuses into most cells and tissues, including the heart, kidney, and small intestine, whereas ERT is only taken up in a subset of organs, with the highest concentration in the liver and spleen, and limited to no concentrations in the heart, kidney, and small intestine.⁷⁴ GALAFOLD has also been associated with greater reductions in left ventricular mass index (LVMI) in Fabry patients with left hypertrophy, or LVH, than ERT.⁷⁵ GALAFOLD has also shown comparable results to ERT in stabilizing, or slowing the rate of decline of, renal function (as measured by annualized change in eGFR, among other biomarkers).⁷⁶

72. **Fourth**, treatment with GALAFOLD has demonstrated effective GL-3 clearance from the podocyte, “an important and relatively ERT-resistant glomerular cell.”⁷⁷

73. In addition, even after GALAFOLD’s approval, based on my experience, patients with previously unknown GLA mutations continued to require treatment. Prior to the inventions claimed in the Engineered Mutations Patent, I understand that it was unknown whether the engineered mutations, including the claimed engineered mutations, Y184S, N228H, and T412I,

⁷³ See, e.g., Wu, Y. *et al.*, (2021) Migalastat Tissue Distribution: Extrapolation from Mice to Humans Using Pharmacokinetic Modeling & Comparison with Agalsidase Beta Tissue Distribution in Mice, *Clinical Pharmacology Drug Dev.* **10**:1075–88 (ATGAL_10161482 at -492).

⁷⁴ See, e.g., *id.*

⁷⁵ ’388 Patent at col. 51:11–59; ’489 Patent at col. 43:1–18; ’490 Patent at col. 43:1–18.

⁷⁶ ’388 Patent at col. 50:52–51:10; ’489 Patent at col. 42:10–42; ’490 Patent at col. 42:10–42.

⁷⁷ Mauer, M. *et al.*, (2017) Reduction of Podocyte Globotriaosylceramide Content in Adult Male Patients with Fabry Disease with Amenable GLA Mutations Following 6 Months of Migalastat Treatment, *J. Med. Genet.* **54**:781 (ATGAL_06818690 at -690).

were associated with Fabry disease let alone whether patients with such mutations could be treated with GALAFOLD. Upon diagnosing a patient as having Fabry disease associated with a previously unknown mutation, a physician such as myself would have to contact Amicus and request that the amenability of the new mutation be ascertained. The testing of a new mutation can take several months. That delay is precious time that the patient is not receiving treatment or is receiving ERT rather than GALAFOLD.⁷⁸

74. There was a long-felt but unmet need for ways to provide treatment options for Fabry disease earlier, prior to disease progression for patients who had mutations that were previously unknown. Early treatment options are important for patients who are far along in disease progression. In addition, early identification of treatment options can be important before patients begin to develop those more severe symptoms and for patients whose disease progresses faster than others and have a critical window to get maximum benefits from treatment.⁷⁹ The inventions described in the Asserted Claims of the Engineered Mutations Patent met this unmet need by providing earlier treatment options for this new population of patients, specifically for patients with previously unknown mutations, including the patients with the mutations in the Asserted Claims.

B. Failures of Others

75. It is my opinion that the non-obviousness of the Asserted Claims of the Reassessment Mutations Patents is supported by the fact that others tried and failed to develop the inventions of the Asserted Claims, namely the failures to find a better (for example, non-

⁷⁸ E. Benjamin Dep. Tr. at 47:1-5.

⁷⁹ See, e.g., '164 Patent, 24:35-37; Apr. 2023 Galafold: Awareness, Trial & Usage – US Wave 6 (ATGAL_08445866 at -886).

ERT) method of effectively treating Fabry patients with certain α -Gal A mutations. My opinion is based on failures by others who tried to develop and commercialize a pharmaceutical chaperone product such as migalastat for the treatment of LSDs such as Fabry disease and the failures of others who tried to develop reliable and accurate methods of determining which patients, or mutations, will respond to treatment with migalastat. Specifically, Shire Human Genetics Therapies, Inc. (“Shire”) in collaboration with Amicus, and later Glaxo Group Limited (“GSK”) also in collaboration with Amicus, attempted to develop migalastat as a treatment for Fabry disease. However, both Shire and GSK terminated their efforts to develop migalastat and ended their collaborations with Amicus. And ultimately, only Amicus was successful.

76. In 2002, with its founding, Amicus started to investigate a therapeutic strategy that uses migalastat to induce correct folding and to rescue the function of α -Gal A enzyme in Fabry disease patients.⁸⁰ [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

⁸⁰ [REDACTED]

⁸¹ [REDACTED]

[REDACTED]

77. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

78. By December 13, 2006, Amicus was conducting Phase 2 trials to evaluate migalastat as a treatment for Fabry disease.⁸⁵ [REDACTED]

[REDACTED]

79. On November 8, 2007, Shire and Amicus announced that they had entered a strategic collaboration to jointly develop a treatment for Fabry disease called Amigal (migalastat hydrochloride).⁸⁷ The collaboration also included the joint development of two other pharmacological chaperone compounds for lysosomal storage disorders: Plicera (isofagomine

⁸² *Id.* at -871.

⁸³ [REDACTED]

⁸⁴ December 13, 2006 FDA Memorandum of Meeting Minutes (ATGAL_00016985 at -992).

⁸⁵ *Id.*

⁸⁶ *Id.*

⁸⁷ Nov. 8, 2007 Amicus Announcement, Amicus Therapeutics and Shire plc Enter Into \$440 Million Ex-US Licensing Agreement to Develop and Commercialize Amigal™, Plicera™, and AT2220 (ATGAL_08418426 at -426).

tartrate) for the treatment of Gaucher disease, and AT2220 (deoxynojirimycin) for the treatment of Pompe disease.⁸⁸

80.

81.

On October 23, 2009, Amicus initiated the first proposed Phase 3 study, AT1001-0011

88 *Id.*

⁸⁹ June 17, 2008 FDA Memorandum of Meeting Minutes (ATGAL_00016985 at -7008–09).

(“the 011 Study”).⁹⁰ The primary objective of this study was to compare the effect of migalastat (123 milligrams of migalastat (equivalent to 150 mg of migalastat hydrochloride)) versus placebo on kidney GL-3.⁹¹ The double-blind, randomized, placebo-controlled study enrolled 67 participants with Fabry disease at 46 sites worldwide.⁹² All participants were naïve to GALAFOLD and ERT or were previously treated with ERT (agalsidase beta or non-U.S. approved agalsidase alfa) and had been off ERT for at least 6 months were randomized in a 1:1 ratio to receive either GALAFOLD 123 mg every other day or placebo for the first 6 months.⁹³ In the second 6 months, all patients were treated with GALAFOLD.⁹⁴ [REDACTED]

[REDACTED]

[REDACTED].⁹⁵ The major efficacy outcome measure of the average number of GL-3 inclusions per kidney interstitial capillary in renal biopsy samples was assessed by light microscopy before and after treatment.⁹⁶

⁹⁰ Study of the Effects of Oral AT1001 (Migalastat Hydrochloride) in Patients With Fabry Disease, ClinicalTrials.gov, <https://clinicaltrials.gov/study/NCT00925301> (ATGAL_10161526 at -526).

⁹¹ *Id.* at -526.

⁹² *Id.*

⁹³ June 2024 GALAFOLD Prescribing Information, Clinical Studies (ATGAL_06388594 at -615).

⁹⁴ *Id.*

⁹⁵ Jan. 14, 2015 Clinical Study Report AT1001-011 (ATGAL_00105350 at -350, -373–74).

⁹⁶ June 2024 GALAFOLD Prescribing Information, Clinical Studies (ATGAL_06388594 at -616).

82. Soon after the initiation of the first Phase 3 trial, however, on October 29, 2009, Shire-Amicus terminated their collaboration.⁹⁷ Shortly before the collaboration ended, Amicus suspended enrollment for a Phase 2 clinical trial for another pharmacological chaperone drug, AT2220, for Pompe Disease⁹⁸ and subsequently announced disappointing preliminary results of its Phase 2 study with another pharmacological chaperone drug, PliceraTM, for Gaucher Disease.⁹⁹ According to an article by BioCentury at the time, a “Shire spokesperson said the programs have ‘experienced some outcomes that delayed their development,’ and therefore Shire concluded that the risk profile no longer fit the company’s criteria.”¹⁰⁰ [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

⁹⁷ *Amicus Shares Fall on Closed Partnership, Jobs Cuts*, San Diego Union-Tribune (Aug. 29, 2016), <https://www.sandiegouniontribune.com/2009/10/30/amicus-shares-fall-on-closed-partnership-job-cuts/> (ATGAL_10161477 at -477); *Amicus Therapeutics, Shire Deal*, BioCentury (Nov. 2, 2009), <https://www.biocentury.com/article/90279/amicus-therapeutics-shire-deal> (ATGAL_10161428 at -428).

⁹⁸ Feb. 27, 2009 Amicus Announcement, Amicus Therapeutics Suspends Enrollment for Phase 2 Clinical Trial of AT2220 for Pompe Disease (ATGAL_04042962 at -962).

⁹⁹ Oct. 2, 2009 Amicus Announcement, Amicus Therapeutics Announces Preliminary Results of Phase 2 Study with PliceraTM for Gaucher Disease (ATGAL_08837476 at -476).

¹⁰⁰ *Amicus Therapeutics, Shire Deal*, BioCentury (Nov. 2, 2009), <https://www.biocentury.com/article/90279/amicus-therapeutics-shire-deal> (ATGAL_10161428 at -428).

101 [REDACTED]

102 [REDACTED]

83. About a year after the Shire-Amicus collaboration ended, GSK and Amicus announced a collaboration with the same goal of developing and commercializing migalastat, which was still in the 011 Study at the time.¹⁰³

84. [REDACTED]

[REDACTED]¹⁰⁴ The primary objective of the 012 Study was to compare the efficacy and safety of migalastat and ERT in male and female participants with Fabry disease who were currently receiving ERT and who had certain α -Gal A mutations that seemed responsive to migalastat based on the same experimental in vitro assay used for enrollment in the 011 Study.¹⁰⁵ The 012 Study was a randomized, open-label, active-controlled clinical trial of 18 months duration in patients with Fabry disease receiving enzyme replacement therapy who were randomized to either switch to GALAFOLD or continue enzyme replacement therapy.¹⁰⁶

85. On December 10, 2012, the 011 Study data was unblinded, revealing that Amicus-GSK failed to meet the study's endpoints.¹⁰⁷ Out of the 45 evaluable patients, 25

¹⁰³ Oct. 28, 2010 GSK and Amicus Therapeutics Enter Exclusive Worldwide Agreement to Develop and Commercialise Amigal™ for Fabry Disease (ATGAL_10161469 at -469).

¹⁰⁴ Mar. 31, 2016 Clinical Study Report AT1001-012 (ATGAL_00118916 at -917).

¹⁰⁵ Study to Compare the Efficacy and Safety of Oral AT1001 and Enzyme Replacement Therapy in Patients with Fabry Disease, ClinicalTrials.gov, <https://clinicaltrials.gov/study/NCT01218659> (ATGAL_10161573 at -573).

¹⁰⁶ June 2024 GALAFOLD Prescribing Information, Clinical Trials Experience (ATGAL_06388594 at -596).

¹⁰⁷ Oct. 26, 2016 Migalastat Type B Meeting (ATGAL_01149299 at -305); *see also* Dec. 19, 2012 GSK-Amicus Press Release, Amicus Therapeutics and GlaxoSmithKline Announce Top Line 6-Month Primary Treatment Period Results from First Phase 3 Fabry Monotherapy Study (ATGAL_01109151 at -151-52).

received GALAFOLD (18 females, 7 males) and 20 received placebo (11 females, 9 males).¹⁰⁸

As shown below, there was not a significant difference between the group receiving

GALAFOLD and the group receiving placebo¹⁰⁹:

Table 3: Changes from Baseline to Month 6 in Average Number of GL-3 Inclusions per KIC in Adults with Fabry Disease with Amenable *GLA* Variants in Study 1 (N = 45)

	GALAFOLD	Placebo
	n/N (%) with $\geq 50\%$ reduction Median change from baseline (range)	n/N (%) with $\geq 50\%$ reduction Median change from baseline (range)
All patients (N = 45)	13/25 (52%) -0.04 (-1.94, 0.26)	9/20 (45%) -0.03 (-1.00, 1.69)
Females (N = 29)	8/18 (44%) -0.02 (-0.46, 0.26)	5/11 (46%) -0.03 (-0.35, 0.10)
Males (N = 16)	5/7 (71%) -1.10 (-1.94, -0.02)	4/9 (44%) -0.03 (-1.00, 1.69)
Patients with baseline GL-3 ≥ 0.3 (N = 17; 9 males, 8 females)	7/9 (78%) -0.91 (-1.94, 0.19)	2/8 (25%) -0.02 (-1.00, 1.69)
Patients with baseline GL-3 < 0.3 (N = 28; 7 males, 21 females)	6/16 (38%) -0.02 (-0.10, 0.26)	7/12 (58%) -0.05 (-0.16, 0.14)

¹⁰⁸ June 2024 GALAFOLD Prescribing Information, Clinical Studies (ATGAL_06388594 at -616); *see also Updated: Amicus Shares Tank on PhIII Failure for Fabry Drug Partnered with GlaxoSmithKline*, Fierce Biotech (Dec. 19, 2012), <https://www.fiercebiotech.com/r-d/updated-amicus-shares-tank-on-phiii-failure-for-fabry-drug-partnered-glaxosmithkline> (ATGAL_10161435 at -435).

¹⁰⁹ June 2024 GALAFOLD Prescribing Information, Clinical Studies (ATGAL_06388594 at -616).

86. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

87. Based on my experience and the experience of my colleagues in the Fabry community, the results of the study were disappointing to providers and patients. A great degree of hope and anticipation were tied to this investigation.¹¹³ For Fabry providers, this initial failure meant that a new therapeutic option would not be available for patients. Providers were aware that the existing and only therapy, ERT, had inherent limitations and did not address all the existing needs of the Fabry community, as discussed above in Section XI.A. For Fabry patients, this initial failure meant being relegated to ERT as the only approved therapy. [REDACTED]

[REDACTED]¹¹⁴ [REDACTED]

110 [REDACTED]

[REDACTED]

111 [REDACTED]

112 [REDACTED]

[REDACTED]

¹¹³ See, e.g., Oct. 28, 2010 GSK and Amicus Therapeutics Enter Exclusive Worldwide Agreement to Develop and Commercialise AmigalTM for Fabry Disease (ATGAL_10161469 at - 471–72).

114 [REDACTED]

[REDACTED]

[REDACTED] ¹¹⁵

88. [REDACTED] in November 2013, GSK dropped out of the development collaboration.¹¹⁶

89. The unblinding of the 011 Study, showing that Amicus-GSK failed to meet its endpoints, and both GSK's and Shire's exits from their respective collaborations with Amicus, demonstrate that others failed to find a better (e.g., non-ERT) method of effectively treating Fabry patients with certain α -Gal A mutations, before the inventions claimed in the Asserted Claims of the Reassessment Mutations Patents. There is thus a nexus between these failures and the inventions claimed in the Asserted Claims of the Reassessment Mutations Patents.

90. Because of these failures, the community of providers and patients were disappointed as the trial represented another opportunity for enhanced treatment options in Fabry and potentially better outcomes via an oral therapy. There were concerns that this initial failure would result in industry abandoning the concept completely. As such, many patients and providers felt that the likelihood of GALAFOLD making it to market for clinical use had decreased significantly.¹¹⁷

¹¹⁵ See, e.g., *id.*; Berry, L. *et al.*, (2024) Patient-Reported Experience with Fabry Disease & Its Management in the Real-World Setting: Results from a Double-Blind, Cross-Sectional Survey of 280 Respondents, *Orphanet J. Rare Diseases* **19**:153 (ATGAL_10161416 at -417).

¹¹⁶ Nov. 20, 2013 GSK-Amicus Press Release, Amicus Therapeutics and GSK Announce Revised Fabry Agreement (ATGAL_00992277 at -227); John Carroll, *GlaxoSmithKline Politely Dumps \$230M Fabry Drug Deal with Amicus*, Fierce Biotech (Nov. 20, 2013), <https://www.fiercebiotech.com/financials/glaxosmithkline-politely-dumps-230m-fabry-drug-deal-amicus> (ATGAL_10161437 at -437).

¹¹⁷ See, e.g., Dec. 19, 2012 GSK-Amicus Press Release, Amicus Therapeutics and GlaxoSmithKline Announce Top Line 6-Month Primary Treatment Period Results from First Phase 3 Fabry Monotherapy Study (ATGAL_01109151 at -151–52); *Updated: Amicus Shares*

91. Additionally, the 15-year lag between approval of the ERT treatment FABRAZYME and approval of Amicus's non-ERT treatment GALAFOLD is further evidence of the failure of others to develop a non-ERT treatment for Fabry disease. In 2003, FDA approved Genzyme's FABRAZYME (agalsidase beta).¹¹⁸ FABRAZYME is an enzyme replacement therapy and was the first approved Fabry treatment.¹¹⁹ It was not until over 15 years later, on August 10, 2018, FDA approved Amicus's GALAFOLD (migalastat).¹²⁰ GALAFOLD is a small molecule and was the first approved oral therapy approved for Fabry treatment.¹²¹ Based on clinicaltrials.gov, between April 24, 2003 and August 10, 2018, 118 clinical trials began that were focused on Fabry disease, 17 of which were by Amicus.¹²² This is for a disease

Tank on PhIII Failure for Fabry Drug Partnered with GlaxoSmithKline, Fierce Biotech (Dec. 19, 2012), <https://www.fiercebiotech.com/r-d/updated-amicus-shares-tank-on-phiii-failure-for-fabry-drug-partnered-glaxosmithkline> (ATGAL_10161435 at -435); May 22, 2013 FDA Memorandum of Meeting Minutes (ATGAL_00632220 at -221-22); May 22, 2013 Dr. Jeff Castelli's Internal Notes on May 22 FDA Meeting ("next steps in light of a 'failed' trial") (ATGAL_00662884 at -884); Nov. 20, 2013 GSK-Amicus Press Release, Amicus Therapeutics and GSK Announce Revised Fabry Agreement (ATGAL_00992277 at -227); John Carroll, *GlaxoSmithKlein Politely Dumps \$230M Fabry Drug Deal with Amicus*, Fierce Biotech (Nov. 20, 2013), <https://www.fiercebiotech.com/financials/glaxosmithkline-politely-dumps-230m-fabry-drug-deal-amicus> (ATGAL_10161437 at -437).

¹¹⁸ May 2010 FABRAZYME Prescribing Information (ATGAL_09687616 at -616).

¹¹⁹ *See id.*

¹²⁰ June 2024 GALAFOLD Prescribing Information (ATGAL_06388594 at -594); Aug. 10, 2018 FDA News Release, FDA Approves New Treatment for a Rare Genetic Disorder, Fabry Disease (ATGAL_09880475 at -475).

¹²¹ *Id.*; Moran, N., (2018) FDA Approves Galafold, a Triumph for Amicus, *Nat. Biotechnol.* **36**:91 (ATGAL_10161450 at -450).

¹²² *Search Results Surrounding Fabry Studies*, ClinicalTrials.gov, https://clinicaltrials.gov/search?cond=fabry&limit=100&start=2003-04-24_2018-08-10 (ATGAL_10161541 at -541-71).

impacting what has been estimated at about 50,000 people in the U.S.¹²³ Given the efforts by others to develop alternative treatment options, the long delay between the approval of FABRAZYME and GALAFOLD is indicative of the failure of others.

C. Industry Praise

92. In my opinion, the non-obviousness of the Asserted Claims of the Reassessment Mutations Patents is supported by the scientific and medical community's praise for Amicus's work in successfully developing an alternative oral medication treatment to ERT for effectively treating Fabry patients with certain α -Gal A mutations.

93. Amicus has received multiple awards for GALAFOLD. For example, in 2018, Amicus received the prestigious UK Prix Galien Medal for Innovative Product for GALAFOLD. Additionally, Amicus received the National Organization for Rare Disorders' Industry Innovation Award for GALAFOLD in 2019. Each is explained further below.

94. Amicus has also seen industry praise reflected in its internal research on how healthcare providers' opinions on GALAFOLD have developed year-over-year since market approval. Based on my experience, patients also appreciate GALAFOLD for its ease to self-administer, which leads to a higher quality of life as compared to treatment by ERT, which must be administered intravenously every other week, and thus there is a nexus between this praise and the inventions of the Asserted Claims of the Reassessment Mutations Patents.

95. 2019 National Organization for Rare Disorders Industry Innovation Award.

The National Organization for Rare Disorders ("NORD") is "the first national nonprofit to represent all individuals and families affected by rare disease. Today [they]'re the only

¹²³ *Frequently Asked Questions: How Common Is Fabry Disease?*, National Fabry Disease Foundation, <https://www.fabrydisease.org/faq/115-how-common-is-fabry-disease> (ATGAL_10161460 at -460).

organization working at the intersection of care, research, policy, and community for all rare diseases.”¹²⁴ “The Rare Impact Awards is an event hosted annually by NORD, the leading independent advocacy organization committed to the identification, treatment and cure of rare disorders through programs of education, advocacy, research and patient services.”¹²⁵ The Rare Impact Awards, including the Industry Innovation Award, are considered prestigious in the rare disease community.¹²⁶ In 2019, Amicus was awarded the Industry Innovation Award in acknowledgement of its “extraordinary work to help improve and save” the lives of patients with rare diseases such as Fabry disease, and to “honor [the awardees] for their stellar contributions to the community.”¹²⁷

96. The 2019 NORD Industry Innovation Award reflects Amicus’s inventions claimed in the Asserted Claims of the Reassessment Mutations Patents, and thus there is a nexus between this praise and the inventions of the Asserted Claims of the Reassessment Mutations Patents. Amicus received the award due to its work in developing GALAFOLD as a treatment

¹²⁴ *About Us: Who We Are*, National Organization for Rare Disorders, <https://rarediseases.org/about-us/> (ATGAL_10161413 at -414).

¹²⁵ *NORD Announces Honorees for 2019 Rare Impact Award*, National Organization for Rare Disorders (Mar. 12, 2019), <https://rarediseases.org/nord-announces-honorees-for-2019-rare-impact-awards/> (ATGAL_10161463 at -463).

¹²⁶ *See, e.g.*, Aug. 1, 2019 Email from J. Gershkowiz to All Amicus Employees Regarding Giant Leap for Amicus (ATGAL_09027547 at -547).

¹²⁷ *NORD Announces Honorees for 2019 Rare Impact Award*, National Organization for Rare Disorders (Mar. 12, 2019), <https://rarediseases.org/nord-announces-honorees-for-2019-rare-impact-awards/> (ATGAL_10161463 at -463); June 22, 2019 Rare Impact Award Ceremony (ATGAL_10161572 at -572).

for Fabry disease, including Fabry patients having the mutations recited in the Asserted Claims of the Reassessment Mutations Patents.¹²⁸

97. As part of Amicus's development of GALAFOLD, FDA approved the treatment in August 2018.¹²⁹ The label included treatment of Fabry diseases by administering 123 mg of migalastat every other day where the patient has an amenable mutation identified in Table 2 of the label. At the time of approval by FDA, those mutations included¹³⁰:

- **Claim 8 of the '388 Patent:** A13P, A20D, Q57L, G80D, P146S, D175E, K213M, I242F, M267T, A309V, V316I, V316G, P323R, A352G, R356P, T385A, V390M, and G395A;
- **Claim 36 of the '388 Patent:** G80D, P146S, M267T, and R356P;
- **Claim 17 of the '489 Patent:** A13T, N34T, M42K, L54F, P60T, E87D, L89F, I133M, Y123C, H125L, K140T, F145S, P146R, Y152H, D165G, p.M187_S188dup, V199G, M208R, I219L, N224T, Q250R, G261C, G271D, M284V, I303F, D322N, G325R, K326N, G334E, E358D, E358Q, G361E, G375E, T412N and M421V;
- **Claim 23 of the '489 Patent:** L54F, L89F, K140T and G334E; and
- **Claim 9 of the '490 Patent:** I242F.

98. **2018 UK Prix Galien Medal for Innovative Product.** "Galafold (migalastat) was awarded the 2018 UK [United Kingdom] Prix Galien Medal for Innovative Product. The Prix Galien is awarded to companies who have made significant advances in pharmaceutical

¹²⁸ See *NORD Announces Honorees for 2019 Rare Impact Award*, National Organization for Rare Disorders (Mar. 12, 2019), <https://rarediseases.org/nord-announces-honorees-for-2019-rare-impact-awards/> (ATGAL_10161463 at -463); August 2018 GALAFOLD Prescribing Information, Table 2 (ATGAL_09990385 at -391–403).

¹²⁹ August 2018 GALAFOLD Prescribing Information, Table 2 (ATGAL_09990385 at -385).

¹³⁰ See *id.* at -391–403.

research, and is regarded as the highest accolade for biomedical research and development.”¹³¹

“The Prix Galien Awards were founded in France in 1970 to celebrate the endeavours of scientists, researchers and industry to develop innovations that advance the treatment of human disease.”¹³² GALAFOLD was “the first ever orphan drug to win in the Innovative Product category.”¹³³ “The Prix Galien awards are considered by many to be the industry’s equivalent of a Nobel Prize.”¹³⁴

99. The 2018 UK Prix Galien Medal for Innovative Product reflects Amicus’s innovative work claimed in claim 23 of the ’489 Patent and claim 9 of the ’490 Patent, and thus there is a nexus between this praise and the inventions of the Asserted Claims of the Reassessment Mutations Patents. Amicus received the award due to its work in developing GALAFOLD as a treatment for Fabry disease, including Fabry patients having the mutations recited in claim 9 of the ’490 Patent and claim 23 of the ’489 Patent.¹³⁵ In the UK, the Medicines and Healthcare Products Regulatory Agency approved GALAFOLD in May 2016.¹³⁶ That label included treatment of Fabry diseases by administering 123 mg of migalastat every other day where the patient has an amenable mutation identified in Table 2 of the label. At the

¹³¹ Dec. 11, 2018 Amicus Announcement, Amicus Therapeutics Awarded UK Prix Galien Medal for Galafold (Migalastat) (ATGAL_00325069 at -069).

¹³² *Id.*

¹³³ *Id.*

¹³⁴ *Id.*

¹³⁵ *See id.*; GALAFOLD Summary of Product Characteristics (ATGAL_03151057 at -060–67).

¹³⁶ May 31, 2016 Amicus Therapeutics Announces European Commission Approval for Galafold™ (Migalastat) in Patients with Fabry Disease in European Union (ATGAL_07336052 at -052).

time of approval by the Medicines and Healthcare Products Regulatory Agency, those mutations included¹³⁷:

- **Claim 23 of the '489 Patent:** L54F, L89F, K140T, and G334E; and
- **Claim 9 of the '490 Patent:** I242F.

100. **Healthcare Provider Opinions Praising GALAFOLD.** [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

101. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

¹³⁷ GALAFOLD Summary of Product Characteristics (ATGAL_03151057 at -060–67).

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

102. The praise from healthcare providers reflects Amicus's inventions claimed in the Asserted Claims of the Reassessment Mutations Patents, and thus there is a nexus between this praise and the inventions of the Asserted Claims of the Reassessment Mutations Patents. Amicus received the praise due to its work in developing GALAFOLD as a treatment for Fabry disease, including Fabry patients having the mutations recited in the Asserted Claims of the Reassessment Mutations Patents.¹⁴³ [REDACTED]

[REDACTED]

103. FDA approved GALAFOLD in August 2018.¹⁴⁵ The label included treatment of Fabry diseases by administering 123 mg of migalastat every other day where the patient has an amenable mutation identified in Table 2 of the label. At the time of approval by FDA, those mutations included¹⁴⁶:

- **Claim 8 of the '388 Patent:** A13P, A20D, Q57L, G80D, P146S, D175E, K213M, I242F, M267T, A309V, V316I, V316G, P323R, A352G, R356P, T385A, V390M, and G395A;
- **Claim 36 of the '388 Patent:** G80D, P146S, M267T, and R356P;
- **Claim 17 of the '489 Patent:** A13T, N34T, M42K, L54F, P60T, E87D, L89F, I133M, Y123C, H125L, K140T, F145S, P146R, Y152H, D165G, p.M187_S188dup, V199G, M208R, I219L, N224T, Q250R, G261C, G271D, M284V, I303F, D322N, G325R, K326N, G334E, E358D, E358Q, G361E, G375E, T412N and M421V;

¹⁴³ See Apr. 2023 Galafold: Awareness, Trial & Usage – US Wave 6 (ATGAL_08445866 at -866, -869, -878); August 2018 GALAFOLD Prescribing Information, Table 2 (ATGAL_09990385 at -391–403).

¹⁴⁴ [REDACTED]

¹⁴⁵ August 2018 GALAFOLD Prescribing Information, Table 2 (ATGAL_09990385 at -385).

¹⁴⁶ See *id.* at -391–403.

- **Claim 23 of the '489 Patent:** L54F, L89F, K140T and G334E; and
- **Claim 9 of the '490 Patent:** I242F.

I declare under penalty of perjury that the foregoing is true and correct.

Dated: 4/4/2025

A handwritten signature in blue ink, appearing to read "John L. Jefferies", is positioned above a horizontal line.

JOHN L. JEFFERIES, M.D.

EXHIBIT 1

CURRICULUM VITAE

NAME: **John Lynn Jefferies, MD, MPH, MBA, FACC, FAHA, FAAP, FHFSA, FESC, FRCPE**

TITLE: Professor, Clinical Cardiology, Baptist Health Sciences
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BIRTHDATE: March 6, 1970

BIRTHPLACE: Charleston, West Virginia

MARITAL STATUS: Married, two children, John Parker and Caroline Grace Jefferies

CITIZENSHIP: United States

EDUCATION:

1984-1988 Campbell County Comprehensive High School
Jacksboro, Tennessee

1988-1992 University of
Tennessee Knoxville,
Tennessee
B.S. in Microbiology

1992-1996 University of Tennessee College of
Medicine Memphis, Tennessee
M.D.

1996-1997 Intern, Internal Medicine/Pediatrics
University of Kentucky
Lexington, Kentucky
Chairman: James E. Muller, M.D.
Chairman Emeritus: Jacqueline A. Noonan, M.D.

1997-2000 Resident, Internal Medicine/Pediatrics
University of Kentucky
Lexington, Kentucky

Chairman: Jay W. Mason, M.D.
Chairman Emeritus: Jacqueline A. Noonan, M.D.

2000-2001 Master of Public Health
Major: Epidemiology
University of Kentucky
Lexington, Kentucky

2021-2023 Master of Business Administration
Wharton School of Business
Majors: Management, Entrepreneurship & Innovation
University of Pennsylvania
Philadelphia, Pennsylvania

FELLOWSHIP:

2000-2001 General Internal Medicine
University of Kentucky
Lexington, Kentucky
Chairman: Jay W. Mason,
M.D.
(This training was part of training for Master of Public Health degree.)

2001-2006	Combined Adult and Pediatric Fellowship in Cardiology Division of Cardiovascular Medicine Division of Pediatric Cardiology Texas Heart Institute St. Luke's Episcopal Hospital Texas Children's Hospital Baylor College of Medicine Director: James T. Willerson, M.D. Director: Robert J. Hall, M.D. Director: J. Timothy Bricker, M.D. Director: Jeffrey A. Towbin, M.D.
2003-2006	Pediatric Cardiac Transplantation Division of Pediatric Cardiology Texas Children's Hospital Baylor College of Medicine Houston, Texas Director: Jeffrey A. Towbin, M.D.

ACADEMIC POSITION:

2023-present	Professor Cardiovascular Outcomes Center School of Public Health University of Memphis Memphis, TN
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FACULTY POSITIONS:

2006-2010	Assistant Professor Medicine/Adult Cardiovascular Diseases Baylor College of Medicine Texas Institute at St. Luke's Episcopal Hospital Houston, Texas
2006-2010	Assistant Professor Pediatrics/Pediatric Cardiology Texas Children's Hospital Baylor College of Medicine Houston, Texas
2008-2010	Assistant Professor Adult Cardiovascular Diseases and Pediatric Cardiology M.D. Anderson Cancer Center University of Texas Houston, Texas

2010-2015	Associate Professor Medicine/Adult Cardiovascular Diseases Baylor College of Medicine Texas Institute at St. Luke's Episcopal Hospital Houston, Texas
2010-2015	Associate Professor Pediatric Cardiology Cincinnati Children's Hospital Medical Center Cincinnati, Ohio
2015-2018	Professor Adult Cardiovascular Diseases University of Cincinnati Cincinnati, Ohio
2015-2018	Professor Pediatric Cardiology Cincinnati Children's Hospital Medical Center Cincinnati, Ohio
2015-2018	Professor, Division of Human Genetics Cincinnati Children's Hospital Medical Center Cincinnati, Ohio
2018-2023	Professor and Chair (Tenured) The UT Methodist Cardiovascular Institute Adult Cardiovascular Diseases Memphis, TN
2018-2023	Professor Pediatric Cardiology Le Bonheur Children's Hospital Memphis, TN
2018-2023	Professor Preventive Medicine University of Tennessee Memphis, TN
2018-present	Research Member Adult and Pediatric Cardiology St. Jude Children's Research Hospital Memphis, TN
2018-2023	Professor Adult Cardiovascular Diseases and Pediatric Cardiology

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FACULTY SERVICE:

2006-2010	Adult Cardiovascular Diseases Texas Heart Institute Baylor College of Medicine Houston, Texas
2006-2010	Pediatric Cardiac Intensivist Texas Children's Hospital Baylor College of Medicine Houston, Texas
2006-2010	Pediatric Cardiomyopathy Service Texas Children's Hospital Baylor College of Medicine Houston, Texas
2006-2010	Pediatric Cardiac Transplant Service UNOS Certified (2007) Texas Children's Hospital Baylor College of Medicine Houston, Texas
2006-2010	Cardiovascular Genetics Service Texas Children's Hospital Baylor College of Medicine Houston, Texas
2006-2010	Pediatric Cardiologist St. Luke's Episcopal Hospital Baylor College of Medicine Houston, Texas
2006-2010	Cardiologist M.D. Anderson Hospital University of Texas Houston, Texas
2008-2010	Director, Cardiomyopathy/Heart Failure Program Texas Children's Hospital Baylor College of Medicine Houston, Texas
2009-2010	Co-Director, Cardiovascular Genetics Texas Children's Hospital

Baylor College of Medicine
Houston, Texas

2010-present	Director, Advanced Heart Failure and Cardiomyopathy The Heart Institute Cincinnati Children's Hospital Medical Center Cincinnati, Ohio
2010-2011	Medical Director, Cardiac Transplantation The Heart Institute Cincinnati Children's Hospital Medical Center Cincinnati, Ohio
2010-2012	Attending, Advanced Heart Failure Service Ohio Heart and Vascular The Christ Hospital Cincinnati, Ohio
2010-2013	Co-Director, Cardiovascular Genetics The Heart Institute Cincinnati Children's Hospital Medical Center Cincinnati, Ohio
2010-2013	Associate Director, Heart Institute Research Core The Heart Institute Cincinnati Children's Hospital Medical Center Cincinnati, Ohio
2013-2016	Associate Professor, Division of Human Genetics Cincinnati Children's Hospital Medical Center Cincinnati, Ohio

2016-2018	Professor, Adult Cardiovascular Diseases University of Cincinnati Medical Center Cincinnati, OH
2016-2018	Professor, Pediatric Cardiology Cincinnati Children's Hospital Medical Center Cincinnati, OH
2016-2018	Professor, Division of Human Genetics Cincinnati Children's Hospital Medical Center Cincinnati, OH
2016-2018	Cardiology Clinical Consultant Heart Institute Diagnostic Laboratory Cincinnati, OH
2016-2018	Cardiology Consultant Shriners' Hospital Cincinnati, OH
2018-2020	Professor and Chair The UT Methodist Cardiovascular Institute Adult Cardiovascular Diseases Memphis, TN
2018-2023	Professor Pediatric Cardiology Le Bonheur Children's Hospital Memphis, TN
2018-present	Professor Preventive Medicine University of Tennessee Memphis, TN
2020-2023	Director Hub Research Capacity Core TN-CTSI University of Tennessee Health Science Center Memphis, TN
2020-2023	Medical Director Clinical Trial Networks of Tennessee (CTN2) Memphis, TN
2020-2023	Principal Investigator Stern Cardiovascular Foundation 8060 Wolf River Boulevard, Germantown, TN

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LICENSING AGENCY: National Board of Medical Examiners

WORK EXPERIENCE:

2023-2024	Director, Medical Affairs, Cardiovascular Bristol Myers Squibb Key Achievements: Facilitated expansion of customer base; Drove data generation; Increased thought leader awareness; Recruited clinical investigation sites Responsibilities: Data generation, Thought leader education, Product marketing, Sales force education, Alignment of Medical Science Liaisons
2022-present	Chief Scientific Advisor Daxor Corporation Key Achievements: Driver of Multiple Publications; Development of Scientific Advisory Boards; Grant submissions; International Conference Representation Responsibilities: Evidence generation, Education, Publications, Communication with payors, Communication with investors, Overall company strategy
2023-present	Chief Medical Officer Nuwellis Key Achievements: Facilitated improved payor reimbursement, Generated multiple publications; Coordinated national and international meetings; Facilitated expansion of customer base; Facilitated expansion of product in to novel patient populations Responsibilities: Evidence generation, development and implementation of company strategy, Education of providers and payors, Interfacing with governmental agencies

ADDITIONAL TRAINING:

2011	Disney Institute, Human Capital Academy
2012	Core Leadership, Cincinnati Children's Hospital Medical Center
2012	Intermediate Improvement Science (I2S2)
2013	Advanced Improvement Methods (AIMS)

PROFESSIONAL ORGANIZATION MEMBERSHIPS:

1992	Phi Beta Kappa
1992	Phil Kappa Phi
1993	American Medical Association
1997	American Academy of Pediatrics
1997	Kentucky Medical Association
2001	American Heart Association – Silver Heart Member
2001	American College of Cardiology
2001	Irish American Pediatric Society
2004	Adult Congenital Heart Association
2006	Heart Failure Society of America
2006	American Society of Echocardiography

2006	American College of Cardiology
2006	Congenital Heart Disease and Pediatric Cardiology Section
2006	Texas Chapter, American College of Cardiology
2007	Texas Medical Association
2007	Harris County Medical Society
2007	Pediatric Cardiac Intensive Care Society
2007	International Society of Heart and Lung Transplantation
2008	Cambridge Who's Who
2009	Marquis Who's Who in America
2009	Fellow, American Academy of Pediatrics
2009	Fellow, American College of Cardiology
2010	Ohio Chapter, American College of Cardiology
2011	International Cardio-Oncology Society
2011	American College of Physicians, Internal Medicine
2011-present	America's Top Cardiologists
2012-2018	Cincinnati's Top Doctors
2013-present	Best Doctors in America
2013	Cor Vitae, American Heart Association
2013	Fellow, American Heart Association
2013-present	Cincinnati's Top Doctors
2013	Society for Pediatric Research (SPR)
2014-present	Children's Oncology Group (COG)
2014-2018	Cincy Magazine Top Doctors
2014	Best Doctors in America
2014	Heart Failure Society of America Mentoring Program

2014	Fellow, Council on Clinical Cardiology, American Heart Association
2014	Cor Vitae, American Heart Association
2015	Best Doctors in America
2015	Cardio Renal Society of America
2015	Member, Council on Genomic and Precision Medicine, American Heart Association
2015	Cor Vitae, American Heart Association
2016	Fellow, Heart Failure Society of America
2016	Best Doctors in America
2017	America's Best Physicians
2017	Best Doctors in America
2018	Heart Rhythm Society
2018	Best Doctors in America
2018	Tennessee Chapter, American College of Cardiology
2019	Member, Council on Quality of Care and Outcomes Research, American Heart Association
2019	Best Doctors in America
2020	Best Doctors in America
2020	American College of Physicians
2020	European Society of Cardiology
2020	Heart Failure Association of the European Society of Cardiology
2020	Memphis Top Doctors
2020	Castle Connolly Top Doctors
2020	Southern Society of Clinical Investigation
2021	Cor Vitae, American Heart Association
2021	Fellow, Royal College of Physicians of Edinburgh

2021	Fellow, European Society of Cardiology
2021	Castle Connolly Top Doctors
2021	Memphis Top Doctors
2022	Castle Connolly Top Doctors
2022	National Organization of Rare Disorders
2022	Rare Action Network
2023	Castle Connolly Top Doctors
2024	Gold Standard Board Award, American Heart Association

PRECEPTORSHIPS:

Preceptor, Student Advisory Program, Kinkaid High School, Houston, Texas.

Preceptor, Student Pre-Medical Association, Rice University, Houston, Texas.

HONORS AND AWARDS:

Dean's List, University of Tennessee, Knoxville, Tennessee. 1988-1992.

Granny's Award, Campbell County District, LaFollette, Tennessee. July
1992.

Outstanding Resident in Pediatric Cardiology Award, Department of Pediatrics, University of Kentucky,
Lexington, Kentucky. June 1999.

Outstanding Resident in Pediatric Intensive Care Award, Department of Pediatrics, University
of Kentucky, Lexington, Kentucky. June 1999.

Outstanding Resident in Pediatric Nephrology Award, Department of Pediatrics, University of Kentucky,
Lexington, Kentucky. June 2000.

Outstanding Resident Research Award, Department of Internal Medicine, University of
Kentucky, Lexington, Kentucky. June 2000.

Outstanding Teacher Award, Internal Medicine and Pediatrics, University of Kentucky, Lexington,
Kentucky. June 2000.

Young Investigator Award Nominee, American Academy of Pediatrics Meeting. Genetic predictors and reverse remodeling of dilated cardiomyopathy in muscular dystrophy. **Jefferies JL**, Belmont JW, Craigen WJ, Ware SM, Fernbach SD, Neish SR, Smith EO, Towbin JA. October 2004.

Winner, American Academy of Pediatrics Travel Grant. Genetic predictors and reverse remodeling of dilated cardiomyopathy in muscular dystrophy. **Jefferies JL**, Belmont JW, Craigen WJ, Ware SM, Fernbach SD, Neish SR, Smith EO, Towbin JA. October 2004.

Winner, American Academy of Pediatrics Runner-Up Young Investigator Award for Clinical Research. American Academy of Pediatrics Annual Meeting, San Francisco, California. October 2004.

Winner, Bristol Myers-Squibb American College of Cardiology Grant. American College of Cardiology Scientific Sessions, Orlando, Florida. March 2005.

Winner, Irish American Pediatric Society Travel Grant, Philadelphia, Pennsylvania. September 2005.

Winner, Outstanding Lecture Award, Irish American Pediatric Society, Philadelphia, Pennsylvania. September 2005.

Winner, Sponsorship, Heart Failure University, Los Angeles, California. November 2005.

Winner, ACCF Research Fellowship Award, American College of Cardiology Scientific Sessions, New Orleans, Louisiana. March 2007.

Winner, Thrasher New Researcher Award. May 2007.

Executive Coaching and Feedback Program Awardee, Wharton School of Business, University of Pennsylvania. June 2022.

Paul Dudley White International Scholar Award, American Heart Association, November 2022.

PEER REVIEW/ JOURNAL REVIEWER:

2003-present	Reviewer, <i>Texas Heart Institute Journal</i>
2006-present	Reviewer, <i>Circulation</i>
2006-present	Reviewer, <i>Journal of the American College of Cardiology</i>
2006-present	Reviewer, <i>Journal of Heart and Lung Transplantation</i>
2006-present	Reviewer, <i>Pediatrics</i>
2007-present	Reviewer, <i>Congenital Heart Disease</i>

2007-present	Reviewer, <i>Pediatric Transplantation</i>
2008-present	Reviewer, <i>Cardiology</i>
2008-present	Reviewer, <i>International Journal of Cardiology</i>
2009-present	Reviewer, <i>Circulation Journal</i>
2011-present	Reviewer, <i>Journal of Cardiac Failure</i>
2012-present	Reviewer, <i>Circulation Research</i>
2012-present	Reviewer, <i>American Journal of Medical Genetics: Part A</i>
2012-present	Reviewer, <i>Postgraduate Medicine</i>
2013-present	Reviewer, <i>American Journal of Cardiology</i>
2013-present	Reviewer, <i>Canadian Journal of Cardiology</i>
2013	Reviewer, <i>The Efficacy and Mechanism Evaluation (EME) Program, National Institute for Health Research (UK)</i>
2013-present	Reviewer, <i>European Journal of Paediatric Neurology</i>
2013-present	Reviewer, <i>Molecular Genetics and Metabolism</i>
2014-present	Reviewer, <i>Health Research Board</i>
2014-present	Reviewer, <i>World Journal of Pediatrics</i>
2014-present	Reviewer, <i>Italian Journal of Pediatrics</i>
2014-present	Reviewer, <i>The National Medical Research Council (NMRC)</i>
2014-present	Reviewer, <i>Pediatric Nephrology</i>
2014-present	Reviewer, <i>Journal of Inborn Errors of Metabolism and Screening</i>
2014-present	Reviewer, <i>The Journal of Steroid Biochemistry and Molecular Biology</i>
2014-present	Reviewer, <i>American Journal of Cardiovascular Drugs</i>
2014-present	Reviewer, <i>Catheter and Cardiovascular Interventions</i>

2014-present	Reviewer, <i>Journal of Pediatrics</i>
2015-present	Reviewer, <i>JACC Heart Failure</i>
2015-present	Reviewer, <i>Case Reports in Infectious Diseases</i>
2015-present	Reviewer, <i>Journal of Multidisciplinary Healthcare</i>
2015-present	Reviewer, <i>BMJ Case Reports</i>
2015	Reviewer, <i>Wellcome Trust, India Alliance System</i>
2015	Reviewer, <i>BioMed Research International</i>
2015-present	Reviewer, <i>American Heart Journal</i>
2016	Reviewer, <i>Pediatric Academic Societies Workshop</i>
2016-present	Reviewer, <i>Current Medicinal Chemistry</i>
2016	Reviewer, 2016 Heart, Lung, and Vascular Institute Study Section, University of Cincinnati
2016-present	Reviewer, <i>Case Reports in Obstetrics and Gynecology</i>
2016-present	Reviewer, <i>Kidney and Blood Pressure Research</i>
2016-present	Reviewer, <i>Circulation Heart Failure</i>
2016-present	Reviewer, <i>Clinical Science</i>
2016-present	Reviewer, <i>Expert Review of Cardiovascular Therapy</i>
2016-present	Reviewer, <i>Clinical Cardiology</i>
2017-present	Reviewer, <i>Gene</i>
2017-present	Reviewer, <i>Critical Care Medicine</i>
2017-present	Reviewer, <i>JACC Cardiovascular Imaging</i>
2018-present	Reviewer, <i>Heart Rhythm Case Reports</i>
2018-present	Reviewer, <i>Pediatric Research</i>
2018-present	Reviewer, <i>Journal of Pediatric Infectious Diseases</i>

2018-present	Reviewer, Great Ormond Street Children's Charity
2018-present	Reviewer, <i>Journal of Cardiovascular Computed Tomography</i>
2018-present	Reviewer, <i>Molecular Genetics and Metabolism Reports</i>
2018-present	Reviewer, <i>Journal of the American Heart Association</i>
2018	Guest Editor, <i>Journal of the American Heart Association</i>
2018-present	Reviewer, <i>Clinical Epidemiology</i>
2018-present	Reviewer, <i>BMC Cardiovascular Disorders</i>
2018-present	Reviewer, <i>The Lancet Neurology</i>
2018-present	Reviewer, <i>Heart</i>
2018-present	Reviewer, <i>American Journal of Human Genetics</i>
2019-present	Reviewer, <i>Cardio-Oncology</i>
2019-present	Reviewer, <i>Jornal de Pediatria</i>
2019-present	Reviewer, <i>Drug Design, Development and Therapy</i>
2019-present	Reviewer, <i>Case Reports in Pediatrics</i>
2019-present	Reviewer, <i>Nature Communications</i>
2019-present	Reviewer, <i>Digital Biomarkers</i>
2020-present	Reviewer, <i>Journal of the Saudi Heart Association</i>
2020	Reviewer, <i>American Heart Association Scientific Sessions Abstract Committee</i>
2020-present	Reviewer, <i>JACC CardioOncology</i>
2020-present	Reviewer, <i>American Journal of the Medical Sciences</i>
2020-presnet	Reviewer, <i>American Journal of Transplantation</i>
2021-presnet	Reviewer, <i>Open Heart Journal</i>
2021-present	Reviewer, <i>American Journal of Nephrology</i>
2021	Reviewer, <i>American Heart Association Scientific Sessions Abstract Committee</i>
2021-present	Reviewer, <i>Biomolecules</i>

2021-present	Reviewer, <i>Minerva Cardiology and Angiology</i>
2021-present	Reviewer, <i>JACC Case Reports</i>
2022	Reviewer, Dutch Research Council, Open Competition Domain Science
2022	Reviewer, <i>European Society of Cardiology Congress 2022 Abstract Committee</i>
2022	Reviewer, <i>Leukemia and Lymphoma</i>
2022	Reviewer, <i>Expert Opinion on Pharmacotherapy</i>
2023-present	Reviewer, <i>The American Journal of the Medical Sciences</i>
2023	Reviewer, <i>American Heart Association Scientific Sessions Abstract Committee</i>
2023-present	Reviewer, <i>Journal of the American College of Cardiology Asia</i>
2024-present	Reviewer, <i>JACC: Clinical Electrophysiology</i>
2024-present	Reviewer, <i>Future Rare Diseases</i>
2024-present	Reviewer, <i>JACC: Basic to Translational Research</i>
2024-present	Reviewer, <i>Journal of Medical Case Reports</i>

SERVICE COMMITTEES:

1997	Cardiology Section Review Committee Department of Internal Medicine University of Kentucky
2007-2010	Institutional Review Board Baylor College of Medicine
2009-2010	Committee on Scientific Integrity Baylor College of Medicine
2009-2010	Faculty Research and Fellowship Support Committee Baylor College of Medicine

2009-2010	International Activities Committee Baylor College of Medicine
2010-present	Scholarship Oversight Committee Cincinnati Children's Hospital Medical Center
2011-present	Internal Advisory Committee Program Project Grant "Mechanisms and Clinical Phenotypes of Arrhythmogenic Cardiomyopathy" Cincinnati Children's Hospital Medical Center
2012-present	Data Safety Monitoring Board Clinical Research Study "An Open-Label Trial to Determine the Effect of Losartan Potassium Tablets in Subjects with Eosinophilic Esophagitis (EoE) With or Without a Connective Tissue Disorder" Cincinnati Children's Hospital Medical Center
2012-present	Research Advisory Committee Cincinnati Children's Hospital Medical Center
2012-2017	Ohio-ACC Board of Trustees Ohio American College of Cardiology
2012-present	Chair, Pediatric Heart Failure Initiative Healthcare Accreditation Colloquium
2013-2014	Committee Member, Thesis: Allyson Sommers
2013-present	Member, Adult Care Steering Committee, Cincinnati Children's Hospital
2013	Greater Cincinnati World Affairs Council – US Department of State International Visitor Leadership Program
2014-present	ACHD Steering Committee – Cincinnati Children's Hospital Medical Center 2014-present American College of Cardiology Careers in Heart Failure and Transplant Work Group
2015-present	Member, Heart Institute Tissue Biorepository Steering Committee 2015-present Member, Heart Failure Society of America Development Committee Heart Failure Society of America
2016-present	Member, Careers in Heart Failure Work Group American College of Cardiology
2018-present	Member, Innovative Project Award Committee

American Heart Association

2018 Mentor, American Heart Association Mentoring Program Mentee: Shahnawaz Amdani

2018 Co-Chair, Search Committee for Chief of Pulmonary Medicine/Critical Care University of Tennessee Health Science Center

2018-present Fellowship Recruitment Committee
University of Tennessee Health Science Center

2018-present Clinical Trials Network of Tennessee (CTN2) Board of Directors

2018-present Committee Member
Memphis Institute of Regenerative Medicine

2018-2021 Member, Heart Failure and Transplant Section Leadership Council American College of Cardiology

2018 Member, Search Committee for Cardiovascular Physiology Faculty University of Tennessee Health Science Center

2019-present Chair, Ambulatory Steering Committee, Methodist Healthcare System
2019-present Member, Tennessee American College of Cardiology Council

2019-present Member, Innovation Section, American College of Cardiology

2019-present Member, Cardiovascular Management Section, American College of Cardiology

2019-present Member, Heart Failure Self-Assessment Program Performance Question Committee

2019-present Member, Federal Cardiology Section, American College of Cardiology

2020-present Member, Methodist Le Bonheur Healthcare System Cardiology Peer Review Committee

2020-present Member, Clinical Trials Network of Tennessee (CTN2), Expert Board, Cardiac Failure

2020-present Deputy Director, Heart Failure Self-Assessment Performance Question Committee

2020-2021 Interim Medical Director, Clinical Trials Network of Tennessee (CTN2)

2020-2021	Member, Clinical Trials Industry Advisory Committee University of Tennessee Health Science Center
2021-present	Member, Clinical Trials Governance Board University of Tennessee Health Science Center
2021-present	Member, Lions Club, Mid-South Chapter
2021-present	Member, Operational Strategic Plan for Research Committee, Cardio-Renal and Vascular Disease Workgroup University of Tennessee Health Science Center
2021-present	Member, Methodist Le Bonheur Healthcare System Committee for American College of Cardiology Accreditation
2021	American Heart Association Heart Walk, Top Coach
2021	American College of Cardiology, Board of Governors Book Club
2021	American College of Cardiology, Board of Governors Restrictive Covenant Work Group
2021-2023	Board Member, American Heart Association Mid-South
2021-present	Mentor, HBCU Scholars Program, American Heart Association
2021-2022	Member, SJLIFE Leadership Team
2022	Member, Childhood Cancer Survivorship Program Team
2022-present	Advisor, Cardiology Interest Group, University of Tennessee Health Science Center
2022-present	Member, American College of Cardiology, Board of Governors Advocacy Group
2022	Member, Le Bonheur Children's Hospital Research Program
2023	American College of Cardiology Board of Governors Mentorship Program
2024	American Heart Association Fellowship Cardiomyopathy Grant Program Peer Review

EDITORIAL BOARDS:

2009-present	Editorial Board Member <i>Texas Heart Institute Journal</i>
2015-present	Editorial Board Member <i>PLOS ONE</i>
2015-present	Editorial Board Member <i>Journal of Cardiac Failure</i>
2018-present	Editorial Board Member <i>Journal of the American Heart Association</i>
2019-present	Associate Editor <i>BMC Cardiovascular Disorders</i>
2019	Guest Editor <i>Journal of the American Heart Association</i>
2020-present	Editorial Board Member <i>ACC.org</i>
2020-present	Lead Editor <i>ACC.org Heart Failure and Cardiomyopathies</i>
2020	Guest Editor <i>Journal of the American College of Cardiology</i>
2020	Guest Editor <i>Journal of the American Heart Association</i>
2020-present	Editorial Board Member <i>American Journal of Cardiology</i>
2021	Guest Editor <i>Journal of the American Heart Association</i>
2021-present	Editorial Board Member <i>Journal of Cardiovascular Disease and Development</i>
2021-present	Section Board, Acquired Heart Disease <i>Journal of Cardiovascular Disease and Development</i>
2021-present	Section Board, Genetics <i>Journal of Cardiovascular Disease and Development</i>
2021-present	Section Board, Epidemiology, Lifestyle, and Cardiovascular Health

Journal of Cardiovascular Disease and Development

2022-present Guest Editor and Editorial Board Member
Journal of the American Heart Association

GRANT APPLICATION REVIEWER:

2010-present Grant Application Reviewer
Barth Syndrome Foundation

2018 Grant Application Reviewer
Great Ormond Street Hospital Children's Charity

STUDY SECTIONS:

2021 Member, American Heart Association Cardiomyopathy Fellowship Peer
Review Committee

2021 Member, American Heart Association Strategically Focused Research
Network (SFRN), Cardio-Oncology Basic Peer Review Committee

ADVISORY BOARDS:

2013-present Korey Stringer Institute
Medical Advisory Board

2013-present The Dystrophic Epidermolysis Bullosa Research Association of
America Medical Advisory Board

2015 Medtronic CRHF
Heart Failure Advisory Board

2015-present Barth Syndrome Foundation
International Scientific and Medical Advisory Board

2024-present Harvard Business Review
Advisory Council

BOARD MEMBERSHIPS:

2023-present The Able Channel, Board of Directors

REGISTRY BOARDS, STUDY BOARDS, AND STUDY NETWORKS:

2009-present	Steering Committee Pediatric Cardiomyopathy Registry Funded by NHLBI
2013-present	Chronic Kidney Disease in Children Prospective Cohort Study (CKiD) Cardiovascular Subcommittee
2020-present	Cardiology Oncology Informatics Network (COIN)

MEDICAL MONITOR:

2015-2018	Syncardia 50cc Temporary Total Artificial Heart (TAH-T) as a Bridge to Transplant (BTT)
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SPORTS CARDIOLOGY	Team Cardiologist, <i>Memphis Grizzlies</i> Team Cardiologist, <i>FC 901</i> Team Cardiologist, <i>Memphis Redbirds</i>
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GRANTS AND STUDIES AWARDED:

Active Grants:

2023-2027	Investigator 5RO1CA261834-02 Early identification of childhood cancer survivors at high risk for late onset cardiomyopathy: An artificial intelligence approach using electrocardiography Oguz Akbilgic (PI) Amount: \$2,294,652
2024-2028	Investigator 1R01HL173881-01 Developing and validating race specific cardiomyopathy risk prediction models and African-American survivors of childhood cancer Yadav Sapkota (PI) Amount: \$4,176,076

Previous Grants

2020-2023	Principal Investigator
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1 UO1 CA246570-01A1

Telehealth based exercise intervention to improve functional capacity in survivors of childhood cancer with significantly limited exercise tolerance

Amount: \$2,101,865

2021-2023

Principal Investigator

Randomized controlled pivotal trial of autologous bone marrow mononuclear cells using the CardiAMP Cell Therapy system in patients with post-myocardial infarction heart failure (Cardi-AMP Heart Failure Trial)

Sponsor: BioCardia

Amount: TBD

2021-2023

Principal Investigator

Phase 3, randomized, placebo-controlled, efficacy and safety study VERU-111 for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in patients at high risk for acute respiratory distress syndrome (ARDS)

Sponsor: Veru

Amount: TBD

2021-2023

Principal Investigator

An exploratory, open-label, proof-of-concept, phase 2a study of mavacamten (MYK-461) in participants with heart failure with preserved ejection fraction (HFpEF) and chronic elevation of cardiac troponin I and/or NT-proBNP

Sponsor: Myokardia

Amount: TBD

2021-2022

Principal Investigator

Myocardial infarction detection via automated EKG analysis

Sponsor: HeartBeam

Amount: TBD

2021-2023

Principal Investigator

A double-blind, placebo-controlled, randomized, multicenter, phase 2 study assessing the safety, tolerability, and efficacy of IONIS-AGT-LRX, an antisense inhibitor of angiotensinogen production, administered subcutaneously over 12 weeks in patients with chronic heart failure with reduced ejection fraction

Sponsor: Ionis Pharmaceuticals

Amount: TBD

2021-2023

Investigator

Tennessee Heart Health Network

Sponsor: Agency for Healthcare Research and Quality (AHRQ)

Amount: \$4,500,000

2021-2023	<p>Principal Investigator A randomized, double-blind, placebo-controlled, phase 3 study comparing the efficacy and safety of tirzepatide versus placebo in patients with heart failure with preserved ejection fraction and obesity (obesity-related HFpEF) Sponsor: Eli Lilly Amount: TBD</p>
2021	<p>Investigator HCM Academy Education of providers across multiple specialties in the diagnosis and care of hypertrophic cardiomyopathy Sponsor: Bristol-Myers-Squibb Sponsor: Sanofi Genzyme Amount: TBD</p>
2021-2022	<p>Investigator Adult Congenital & Pediatric Cardiology Virtual Career Day Sponsor: American College of Cardiology Amount: \$6,000</p>
2020-2023	<p>Principal Investigator 1 UO1 CA246570-01A1 Telehealth based exercise intervention to improve functional capacity in survivors of childhood cancer with significantly limited exercise tolerance Amount: \$2,101,865</p>
2020-2021	<p>Principal Investigator Aquadex SmartFlow™ System for Management of Congestive Heart Failure: A Single Site Experience Sponsor: CHF Solutions Amount: \$6,000</p>
2019-2022	<p>Investigator A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Effects of INL1 (Trientine) in Patients with Heart Failure and Reduced Ejection Fraction Sponsor: Innolife Amount: \$125, 730</p>
2020-2023	<p>Investigator Hemodynamic-GUIDEd Management of Heart Failure (GUIDE-HF) Sponsor: Abbott Amount: \$59,300</p>

2020-2022	Collaborator 7R01HL141345-02 SCARNA Modified Induced Pluripotent Stem Cell Derived Cardiomyocytes or Exosomes Therapy for Chronic Ischemic Cardiomyopathy Patients Amount: \$1,140,000
2020-2023	Principal Investigator A Long Term Extension Study of Mavacamten (MYK-461) in Adults with Hypertrophic Cardiomyopathy Who Have Completed the MAVERICK-HCM (MYK-461-006) or EXPLORER-HCM (MYK-461-005) Trials (MAVA-LTE) Sponsor: Myokardia Amount: TBD
2020-2022	Principal Investigator RELIEVE-HF TRIAL: REducing Lung congestion symptoms using the v-wave shunt in adVancEd Heart Failure Sponsor: V-Wave Amount: TBD
2020-2023	Principal Investigator Algorithm Using LINQ Sensors for Evaluation and Treatment of Heart Failure (ALLEVIATE-HF) Sponsor: Medtronic Amount: TBD
2020-2022	Principal Investigator Dapagliflozin in Respiratory Failure Patients With COVID-19 (DARE-19) Sponsor: AstraZeneca Amount: TBD
2020-2021	Principal Investigator Merlin Insight Engine Sponsor: Abbott Amount: \$40,000
2020-2021	Principal Investigator Safety, Tolerability, and Efficacy of Anti-Spike (S) SARS-CoV-2 Monoclonal Antibodies for the Treatment of Ambulatory Adult Patients With COVID-19 (2067) Sponsor: Regeneron Amount: TBD

- 2021-2024 **Principal Investigator**
Changes in NT-proBNP and outcomes, safety, and tolerability in HFpEF patients with acute decompensated heart failure (ADHF) who have been stabilized during hospitalization and initiated in hospital or within 30 days post discharge (PARAGLIDE-HF)
Sponsor: Novartis
Amount: TBD
- 2020-2021 **Principal Investigator**
Study Assessing the Efficacy and Safety of Anti-Spike SARS-CoV2 Monoclonal Antibodies for Prevention of SARS-CoV2 Infection in Asymptomatic Healthy Adults and Adolescents Who Are Household Contacts to an Individual with a Positive SARS-CoV2 RT-PCR Assay
Sponsor: Regeneron
Amount: TBD
- 2021-2023 **Principal Investigator**
An Exploratory, Open-Label, Proof of Concept, Phase 2a Study of Mavacamten in (MYK-461) in Participants With Heart Failure with Preserved Ejection Fraction (HFpEF) and Chronic Elevation of Troponin I and/or NT-ProBNP
Sponsor: MyoKardia
Amount: TBD
- 2020-2022 **Investigator**
Increasing Clinician's Suspicion for TTR
Amyloidosis
Sponsor: Pfizer
Amount: \$24, 560
- 2020-2022 **Principal Investigator**
Two part (double-blind inclisiran versus placebo [Year 1] followed by open-label inclisiran [Year 2] randomized multicenter study to evaluate safety, tolerability, and efficacy of inclisiran in adolescence (12 to less than 18 years) with heterozygous familial hypercholesterolemia and elevated LDL-cholesterol (ORION-16)
Sponsor: Novartis
Amount: TBD
- 2020-2022 **Principal Investigator**
The PQ Bypass pivotal IDE intra-aRterial stent graft study for occlusive and re-stenotic fem-pop revascularization-2 (TORUS-2)
Sponsor: PQ Bypass
Amount: TBD

2020-2022	Principal Investigator ALN-TTR02-012 A Phase 4 Multicenter Observational Study to Evaluate the Effectiveness of Patisiran in Patients with Polyneuropathy of Hereditary Transthyretin-Mediated Amyloidosis with V122I or T60A mutation Sponsor: Alnylam Amount: TBD
2020-2021	Principal Investigator A Master Protocol Assessing the Safety and Efficacy of Anti-Spike (S) Monoclonal Antibodies for the Treatment of Ambulatory Patients with COVID-19 [Regeneron R10933-10987-COV-2067] Companion Sponsor: Regeneron Amount: TBD
2021-2023	Principal Investigator An Open Label Exploratory Study of Oral MYK-491 in Stable Ambulatory Patients with Primary Dilated Cardiomyopathy Due to Either MYH7 or TTN Variants Sponsor: Myokardia Amount: TBD
2021-2023	Principal Investigator Expanded Access Treatment with Open-Label Pegunigalsidase Alfa for Fabry Patients Sponsor: Chiesi Amount: TBD
2000-2001	Principal Investigator Quality of Life and Social Outcomes of Adults with Congenital Heart Disease Sponsor: Crippled Children's Network / Amount: \$5,000
2003-2005	Principal Investigator The Use of Nesiritide in the Pediatric Heart Failure Population Sponsor: Scios, Inc. / Amount: \$35,000
2006-2008	Principal Investigator A Case History, International, Multicenter Trial to Evaluate the Efficacy and Safety of Cardiolite Myocardial Perfusion Imaging in Pediatrics Patients with Kawasaki Disease Sponsor: Bristol-Myers Squibb
2006-2008	Investigator Reduction of Events with Darbepoetin Alfa in Heart Failure Trial

Sponsor: Amgen

2006-2010 **Primary Site Investigator**
Trial of Beta Blocker Therapy vs Angiotensin II Receptor Blocker Therapy in
Individuals with Marfan Syndrome
Sponsor: Pediatric Heart Network
Amount: \$50,000/year

2007-2010 **Investigator**
International Randomized Double Blind Clinical Study Evaluating the Efficacy
and Safety of Clopidogrel 0.2 mg/kg Once Daily Versus Placebo in Neonates
and Infants with Cyanotic Congenital Heart Disease Palliated with a
Systemic-to-Pulmonary Artery Shunt (e.g. Modified Blalock Taussig Shunt)

2007-2010 **Recipient**
American College of Cardiology
ACCF/Pfizer Research Award
Amount: \$65,000/year (\$195,000 total)

2007-2008 **Recipient**
Thrasher New Researcher
Award Amount: \$26,750

2009-2010 Pediatric Cardiomyopathy Registry Cohort Study; NIH/NHLBI; R01 HL53392-15
Primary Institution: University of Miami
Principal Investigator: Steven Lipshultz, MD
Subcontract Principal Investigator: John Lynn Jefferies, MD, MPH
\$40,000 Direct/\$61,400
Total June 1, 2009-May 31,
2010

2009-2010 **Primary Investigator**
Observational Pilot Study among children hospitalized for acute heart failure
syndrome (AHFS) with volume overload secondary to cardiovascular etiology or
due to post-operative volume-overload (POVO) following cardiopulmonary
bypass (CPB) for surgical repair of a congenital heart defect.
Sponsor: Merck, Inc.
Amount: \$57,635

2009-2010 **Investigator**
National Registry of genetically triggered thoracic aortic aneurysms and
cardiovascular conditions (GENTAC)

2012-2013 **Recipient**
Pediatric Heart Failure Fellowship Funding Support
Funding in the amount of \$15,000.00
The Medtronic Grants and Donations Committee

- 2012-2016 **Investigator – 10% Support**
Title of Project: Cardiac Biomarkers in Pediatric
Cardiomyopathy 1 R01 HL109090-01
Principal Investigator: Steven Lipshultz, M.D.
The major goal of this project is to identify clinically relevant biomarkers in
children with Cardiomyopathies and determine the predictability of outcome.
\$7,235,569.00 Total
July 2012-June 2016
- 2013-2016 **Primary Site Investigator**
Otsuka 156-08-276 A Phase 3b, Multicenter, Open-label, Randomized
Withdrawal Trial of the Effects of Titrated Oral SAMSCA® (Tolvaptan)
on Serum Sodium, Pharmacokinetics, and Safety in Children and
Adolescent Subjects Hospitalized With Euvolemic or Hypervolemic
Hyponatremia
- 2013-2016 **Primary Site Investigator**
Otsuka 156-11-294 A Phase 3b, Multicenter, Extension Follow-up Trial to
Evaluate the Long-term Safety of Children and Adolescent Subjects With
Euvolemic or Hypervolemic Hyponatremia Who Have Previously Participated in
a Trial of Titrated Oral SAMSCA ® (Tolvaptan)
- 2013-2014 **Recipient**
Pediatric Heart Failure Fellowship Funding Support
Funding in the amount of \$15,000.00
The Medtronic Grants and Donations Committee
- 2014-2016 **Investigator**
Phase II randomized, placebo-controlled, double blind clinical trial of valsartan
for attenuating disease evolution in early sarcomeric HCM
- 2014-2016 **Co-Investigator**
Genzyme: A Phase 4, open, label, prospective study in patients with Pompe
Disease to evaluate the efficacy and safety of Alglucosidase Alfa produced at
the 4000 L Scale
- 2014-2016 **Co-Investigator**
GENZYME: A Phase 3/4, Prospective, Multinational, Open-label, Noninferiority
Study of Alglucosidase Alfa Manufactured at the 160 L and 4000 L Scales in
Treatment Naïve Patients with Infantile-Onset Pompe Disease
- 2014-2016 **Co-Investigator**
Genzyme: A Cross-sectional Study of Renal Function in Treatment-naïve, Young
Male Patients with Fabry Disease

2014-2016	Co-Investigator Genzyme: Characterization Of Coronary Artery Disease In Individuals With Mucopolysaccharidoses
2013-2016	Site Investigator NIH-NHLBI RO1 HL111459-01 Principal Investigator, Carolyn Ho, M.D. “HCMNet2: Using Genetics for Early Phenotyping and Prevention of HCM” \$11,304,199 (Total) September 1, 2012-August 31, 2016
2014-2016	Site Investigator – 10% support NIH-NHLBI RO1 HL111459-01 Principal Investigator, Stephen E. Lipshultz, M.D. “Genotype-Phenotype Associations in Pediatric Cardiomyopathies”. \$11,304,199 (Total) September 1, 2012-August 31, 2016
2015-2017	Principal Investigator “Use of Handheld Technology to Enhance Patient Cardiac Care: Development and Assessment of Portable Device Applications to Improve Communication and Resource Utilization in Pediatric Cardiomyopathy” Children’s Heart Association of Cincinnati \$20,000.00 October 1, 2015-November 1, 2017
2014-2016	Co-Investigator Novartis Multicenter, open-label, dose escalation study to evaluate safety, tolerability, and pharmacokinetics of RLX030 in addition to standard of care in pediatric patients from birth to <18 years of age, hospitalized with acute heart failure.
2016-2017	Mentor and Senior Investigator Primary Investigator: Hunter Wilson, M.D. Characterization of the Early Cardiac Phenotype in Anderson-Fabry Disease American Academy of Pediatrics \$3,000.00 December 1, 2016-June 30, 2017
2016-2017	Mentor and Senior Investigator Primary Investigator: Hunter Wilson, M.D. Characterization of the Early Cardiac Phenotype in Anderson-Fabry Disease Cincinnati Children’s Research Fund

\$2,000.00
December 1, 2016-June 30, 2017

2017 **Senior Investigator**
Treatment of non-ambulatory boys and young men with Duchenne muscular dystrophy (DMD) and with resultant respiratory and cardiac dysfunction and skeletal muscle weakness with 5 mg/kg of P-188 NF (Carmaseal-MD™)
Sponsor: Phrixus
\$472,728
August 1, 2017-Aug1, 2019

2015-2017 **Principal Investigator**
A Randomized, Open-label Study of the Safety and Efficacy of Multi-Vessel Intracoronary Delivery of Allogeneic Cardiosphere-Derived Cells in Patients with Cardiomyopathy Secondary to Duchenne Muscular Dystrophy [HOPE-Duchenne (Halt cardiomyOPathyprogrESSION in Duchenne)]
Sponsor: Capricor
Amount: \$510,000
August 18, 2015-August 17, 2017

2015-2018 **Principal Investigator**
SHaRe: The Sarcomeric Human Cardiomyopathies Registry Charter
Sponsor: Myokardia
Amount: \$100,000
December 1, 2015-November 30, 2018

2012-2018 **Investigator**
Title of Project: Cardiac Biomarkers in Pediatric Cardiomyopathy 1 R01 HL109090-01
Principal Investigator: Steven Lipshultz, M.D.
\$7,235,569.00 Total
July 2012-December 2018

2013-2018 **Principal Investigator**
Continuous Arrhythmia Monitoring in Patients With Left Ventricular Noncompaction
Sponsor: Medtronic
Amount: \$50,000
February 1, 2013-December 31, 2018

2013-2018 **Investigator**
NIH-NHLBI RO1 HL111459-01
Principal Investigator, Carolyn Ho, M.D.
HCMNet2: Using Genetics for Early Phenotyping and Prevention of HCM
\$11,304,199 (Total)

September 2012-August 2018

2015-2018

Principal Investigator

A Double-Blind, Placebo-Controlled, Multicenter Study with an Open-Label Extension to Evaluate the Efficacy and Safety of SRP-4045 and SRP-4053 in Patients with Duchenne Muscular Dystrophy

Sponsor: Sarepta

Amount: \$291,207.00

October 14, 2015-October 13, 2018

2016-2018

Principal Investigator

Assessment of Quality of Life, Anxiety, and Depression in Barth Syndrome: Expanding the Scope of Comprehensive Care

Sponsor: Barth Syndrome Foundation

Amount: \$38,730

April 2016-December 2018

2017-2020

Principal Investigator

Multicenter, open-label, study to evaluate safety, tolerability, pharmacokinetics and, pharmacodynamics of LCZ696 followed by a 52-week randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 compared with enalapril in pediatric patients from 1 month to < 18 years of age with heart failure due to systemic left ventricle systolic dysfunction.

Sponsor: Novartis

Amount: \$189,951.00

August 2017-September 2020

2017-2018

Principal Investigator

Evaluation of Clinical Outcome Assessments for Pediatric Heart Failure: Patient Interviews

Sponsor: Novartis

Amount: \$14,952

January 25, 2017-December 2018

2018-2020

Investigator

Clinical study to evaluate mavacamten (MYK-461) in adults with symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM)

Sponsor: Myokardia

Amount: \$375,000

November 2018-December 2020

2017-2020

Principal Investigator

An exploratory, open-label study to assess the effect of P-188 NF

(Carmeseal-MDTM) on safety, on respiratory and cardiac dysfunction and on upper body strength in non-ambulatory patients with Duchenne muscular dystrophy (DMD)

Phrixus Pharmaceuticals, Inc.

Amount: \$998,000

July 2018-December 2020

ADVANCED HEART FAILURE AND TRANSPLANT TRAINEES:

2006-2007	Joseph Rossano, M.D. Chief of Cardiology, Co-Director Cardiac Center Children's Hospital of Philadelphia Philadelphia, Pennsylvania
2008-2009	Ivan Wilmot, M.D. Faculty, Heart Failure and Cardiac Transplantation Pediatric Cardiology Fellowship Director Cincinnati Children's Hospital medical Center Cincinnati, Ohio
2009-2010	Sabrina Law, M.D. Faculty, Heart Failure and Cardiac Transplantation Seattle Children's Hospital Seattle, Washington
2012-2013	Thomas Ryan, M.D., PhD. Faculty, Heart Failure and Cardiac Transplantation Cincinnati Children's Hospital Medical Center Cincinnati, Ohio
2013-2014	John Parent, M.D. Faculty, Heart Failure and Cardiac Transplantation Riley Children's Hospital Indianapolis, IN
2013-2014	Tamara Thomas Bradford, M.D. Faculty, Heart Failure and Cardiac Transplantation Louisiana State University Health New Orleans, LA
2013-2014	Chet Villa, M.D. Faculty, Heart Failure and Cardiac Transplantation Cincinnati Children's Hospital Medical Center Cincinnati, Ohio
2015	Jacob Mathew, M.D.

Faculty, Paediatric Cardiology
The Royal Children's Hospital
Melbourne Melbourne, Australia

2015-2016

Sairah Khan, M.D.
Faculty, Heart Failure and Cardiac
Transplantation Children's National
Washington, DC

2016-2017

Michelle Ploutz, M.D.
Advanced Fellow, Heart Failure and Cardiac
Transplantation University of Utah
Salt Lake City, UT

2016-2017

Bethany Wisotzkey, M.D.
Advanced Fellow, Heart Failure and Cardiac
Transplantation Phoenix Children's Hospital
Phoenix, AZ

2017-2018

Samuel Wittekind, M.D.
Faculty, Heart Failure and Cardiac
Transplantation Cincinnati Children's Hospital
Medical Center Cincinnati, OH

2017-2018

Hugo Martinez, M.D.
Faculty, Heart Failure and Cardiac Transplantation
Le Bonheur Children's Hospital, University of Tennessee Health Science
Center Memphis, TN

RESEARCH MENTORING:

2014

John Shabosky
Medical Student Scholars in Child and Adolescent Health Summer Research
Scholarship
\$2,500

2011-2012

Jaime Echarte-Gonzalez, M.D.
Fellow, Pediatric
Gastroenterology

Fellow, Pediatric Hepatology
Cincinnati Children's Hospital Medical Center

2012-2014

Ahmad Kaddourah, M.D., M.S.

Fellow, Pediatric Nephrology

Fellow, Acute Care Nephrology
Cincinnati Children's Hospital Medical Center

2015-2016 Jaime Silva-Gburek, M.D.

Resident, General Pediatrics
Cincinnati Children's Hospital Medical Center

2016 Randa Newman

Genetic Counselor Graduate Student
University of Cincinnati

2016 Clifford J Chin

Summer Undergraduate Research Fellowship
Student, Washington University, St. Louis,
MO
Research Site: Cincinnati Children's Hospital Medical Center

Project: Sleep Disordered Breathing in Patients With Cardiomyopathy

2016 Hayley Jaeger

Student Achievement in Research and Scholarship (STARS)
University of Cincinnati
Research Site: Cincinnati Children's Hospital Medical Center

2016 Destini Thomas-Hayes

Student Achievement in Research and Scholarship (STARS)
University of Cincinnati
Research Site: Cincinnati Children's Hospital Medical Center

2016 Destini Thomas-Hayes

Ronald E. McNair Postbaccalaureate Achievement Program
University of Cincinnati
Research Site: Cincinnati Children's Hospital Medical Center
Project: Sleep Disordered Breathing in Patients With Cardiomyopathy

2017 Hunter Wilson, MD

Resident, Cincinnati Children's Hospital Medical Center
Research Site, Cincinnati Children's Hospital Medical
Center

Project: Characterization of the Early Cardiac Phenotype in Anderson-
Fabry Disease

2019

Amit Nanda, MD

Resident, University of Tennessee Health Science Center
Research Site, University of Tennessee Health Science
Center

Project: Right Heart Mass in Transit with a Hemorrhagic Pericardial Effusion: A
Diagnostic Dilemma

Project: The Paradoxical Impact of Insurance Status on Interfacility Transfer
Times and Outcomes in Patients with ST-Elevation Myocardial Infarction

Project: A Comparative Analysis of Mitraclip Versus Mitral Valve-In-
Valve Replacement for High-Risk Patients with Severe Mitral
Regurgitation After Transcatheter Aortic Valve Replacement

2019

Joel M Raja, MD

Resident, University of Tennessee Health Science Center
Research Site, University of Tennessee Health Science
Center

Project: Etripamil: Intranasal Calcium Channel Blocker: A Novel
Noninvasive Modality in the Treatment of Paroxysmal Supraventricular
Tachycardia

2020

Aranyak Rawal., MD

Resident, University of Tennessee Health Science Center
Research Site, University of Tennessee Health Science
Center

Project: Arrhythmogenic Ventricular Cardiomyopathy (AVC): Challenges with
Complex Genetics and Variable Phenotypes

Project: Aquadex SmartFlow™ System for Management of Congestive Heart
Failure: A Single Site Experience

Project: Utilization of Automated EKG Interpretation Tool (HeartBeam
iCardiologist Technology) in Detecting Acute Coronary Syndrome (ACS)

in Patients with Chest Pain in the Emergency Department

2020

Miquel Angel Maturana Gonzalez, MD

Resident, University of Tennessee Health Science Center
Research Site, University of Tennessee Health Science
Center

Project: Utilization of Automated EKG Interpretation Tool (HeartBeam
iCardiologist Technology) in Detecting Acute Coronary Syndrome (ACS)
in Patients with Chest Pain in the Emergency Department

2020

Kristina Mouksian, MD

Resident, University of Tennessee Health Science Center
Research Site, University of Tennessee Health Science
Center

Project: Utilization of Automated EKG Interpretation Tool (HeartBeam
iCardiologist Technology) in Detecting Acute Coronary Syndrome (ACS)
in Patients with Chest Pain in the Emergency Department

Project: Amyloidosis: A Novel TTR Mutation Found in an Asian Female

2020

Cody Gubin

Research Assistant
Research Site, University of Tennessee Health Science Center

Project: Aquadex SmartFlow™ System for Management of Congestive Heart
Failure: A Single Site Experience

2020-present

Abdul Aziz Asbeutah, MD

Resident, University of Tennessee Health Science Center
Research Site, University of Tennessee Health Science
Center

Project: Incidence of Liver Cirrhosis Among Patients with a Fontan
Circulation: A Systematic Review of the Literature and Meta-Analysis

2020-present

Amber Thacker, MD

Medical Director of Hospital Medicine, Regional One Health

Assistant Professor, Internal Medicine and Pediatrics, University of
Tennessee Health Science Center
Internal Medicine Residency Program Site Director, Regional One Health

2021-present

Eva Ingram, MD

Resident, University of Tennessee Health Science Center
Research Site, University of Tennessee Health Science Center

2021-present

Brianna Taylor

Undergraduate Student, LeMoyne Owen College
American Heart Association HBCU Scholars Program
Project: Lymphedema in Fabry Disease

2021-present

Jaylynn Lanier

Undergraduate Student, LeMoyne Owen College
American Heart Association HBCU Scholars Program

Project: Psychological Symptoms and Physical Limitations
Among Patients with Hypertrophic Cardiomyopathy

2021-present

Jessica Pender

Undergraduate Student, LeMoyne Owen College
American Heart Association HBCU Scholars Program

Project: Assessment of Quality of Life in Barth Syndrome

2021-present

Nelson Mukuka

Undergraduate Student, LeMoyne Owen College
American Heart Association HBCU Scholars Program

Project: Myocardial Infarction Detection by Automated EKG
Analysis

2021-present

David Wilbanks, MD

Internal Medicine Resident
University of Tennessee Health Science Center
Research Site, University of Tennessee Health Science Center

Project: Psychological symptoms and physical limitations with
hypertrophic cardiomyopathy.

INVITED PRESENTATIONS:

1. "Quality of Life and Social Outcomes in Adults with Congenital Heart Disease." Southern Society of General Internal Medicine. New Orleans, Louisiana. April 2001.
2. "Outcomes in Adult Congenital Heart Disease." Irish American Pediatric Society Annual Meeting, Lexington, Kentucky. October 2001.
3. "Preexcitation." Texas Heart Institute Noon Conference. St. Luke's Episcopal Hospital. Houston, Texas. March 2002.
4. "Myocardial Infarction." Pediatric Cardiology Lecture Series. Texas Children's Hospital. Houston, Texas. June 2002.
5. "Electrocardiographic Changes Due to Chest Trauma, Central Nervous System Injury and Hypothermia." Texas Heart Institute Noon Conference. St. Luke's Episcopal Hospital. Houston, Texas. April 2002.
6. "Heart Failure Guidelines." Texas Heart Institute Noon Conference. St. Luke's Episcopal Hospital. Houston, Texas. March 2003.
7. "Aortopulmonary Shunts: Indications and Associated Morbidity." Pediatric Cardiology Lecture Series. Texas Children's Hospital. Houston, Texas. June 2003.
8. "Pediatric Arrhythmias." Texas Heart Institute Noon Conference. St. Luke's Episcopal Hospital. Houston, Texas. March 2004.
9. "Natriuretic Peptides in the Diagnosis and Management of Pediatric Heart Failure." Pediatric Critical Care Lecture Series. Texas Children's Hospital. Houston, Texas. October 2004.
10. "Acute Coronary Syndromes." Pediatric Cardiology Lecture Series. Texas Children's Hospital. Houston, Texas. December 2004.
11. "Renal Artery Stenosis: Treatment Option." Combined Peripheral Vascular Conference. Texas Heart Institute. St. Luke's Episcopal Hospital. Houston, Texas. January 2005.
12. "Interventions in Lower Extremity Peripheral Arterial Disease: The Possible Role of Cryoplasty." Combined Peripheral Vascular Conference. Texas Heart Institute. St. Luke's Episcopal Hospital. Houston, Texas. February 2005.
13. "Women and Heart Disease: Diagnosis and Prevention." National Council of Jewish Women Greater Houston Section, Congregation Beth Israel Sisterhood. Congregation Beth Israel. Houston, Texas. February 2005.

14. "Percutaneous Therapy for Popliteal Aneurysms." Combined Peripheral Vascular Conference. Texas Heart Institute. St. Luke's Episcopal Hospital. Houston, Texas. March 2005.
15. "Nuclear Medicine: The Basics." Non-Invasive Imaging Conference. Texas Children's Hospital. Houston, Texas. April 2005.
16. "The Use of Cryoplasty in Peripheral Interventions: Part I." Concepts in Contemporary-Cardiology Symposium. Houston, Texas. April 2005.
17. "The Use of Cryoplasty in Peripheral Interventions: Part II." Concepts in Contemporary Cardiology Symposium. Houston, Texas. April 2005.
18. "Pediatric Experience with Nesiritide." Pediatric Cardiology Continuing Education, Mayo Clinic. Rochester, Minnesota. May 2005.
19. "Safety of Nuclear Imaging in Pediatrics." Texas Heart Institute. St. Luke's Episcopal Hospital. Houston, Texas. June 2005.
20. "Diagnosis and Treatment of Myocardial Ischemia in Children." Texas Children's Hospital. Houston, Texas. August 2005.
21. "Localization of Dendritic Cells and Monocytes to the Graft Matrix of Polytetrafluoroethylene Grafts Used in the Palliation of Cyanotic Heart Defects." Irish and American International Pediatric Society Meeting. Philadelphia, Pennsylvania. September 2005.
22. "The Initial Use of Nesiritide in the Pediatric Population." Irish and American International Pediatric Society Meeting. Philadelphia, Pennsylvania. September 2005,
23. "Cardiovascular Genetics: From Bench to Bedside." Invited Lecture, Visiting Professor. University of Kentucky. Lexington, Kentucky. October 2005.
24. "Dystrophinopathies." Invited Lecture, Vanderbilt University. Nashville, Tennessee. November 2005.
25. "Cardiovascular Genetics." Invited Lecture, Cardiology Noon Conference. University of Pennsylvania. Philadelphia, Pennsylvania. January 2006.
26. "The Use of Nesiritide at the Texas Children's Hospital." Invited Lecture, Cardiology 2006: Ninth Annual Update on Pediatric Cardiovascular Disease by Children's Hospital of Philadelphia. Scottsdale, Arizona. February 2006.
27. "Heart Failure Management: New Pharmacologies in the Congenital Armamentarium." Invited Lecture, American College of Cardiology. Atlanta, Georgia. March 2006.
28. "Congenital Echocardiography." Texas Heart Institute Noon Conference, St. Luke's Episcopal Hospital. Houston, Texas. April 2006.
29. "Pharmacotherapy for Heart Failure." Noon Conference, Texas Children's Hospital. Houston,

Texas. September 2006.

30. "The Genetics of Pediatric Cardiomyopathy." Invited Lecture, Ospedale Pediatrico Bambino Gesù. Rome, Italy. September 2006.
31. "Neurohormonal Axis and Use of Natriuretic Peptides." Invited Lecture, The Second International Conference on Heart Failure in Children and Young Adults. Laguna Niguel, California. November 2006.
32. "Novel Medical Therapies for Pediatric Heart Failure." Invited Lecture, Idiopathic and Primary Cardiomyopathy in Children: Research Directions and Strategies Conference. Bethesda, Maryland. January 2007.
33. "Neurodevelopmental Outcomes in Congenital Heart Disease." Neonatology Noon Conference, Texas Children's Hospital. Houston, Texas. March 2007.
34. "Indications for Surgery for Congenital Aortic Stenosis: Children Versus Young Adults." Invited Lecture, American College of Cardiology. New Orleans, Louisiana. March 2007.
35. "Choosing an Academic Mentor." Invited Lecture, American College of Cardiology. New Orleans, Louisiana. March 2007.
36. "Managing Cardiac Disease in Muscular Dystrophy." Muscular Dystrophy Association Seminar. Houston, Texas. April 2007.
37. "Debate: Current Heart Failure Guidelines Should Apply to Adult Congenital Heart Disease Patients: Proponent." Invited Young Investigator, Philadelphia Adult Congenital Heart Disease Conference. Philadelphia, Pennsylvania. June 2007.
38. "Cardiovascular Genetics: From Bench to Bedside." Invited Lecture, Acute Care for the Primary Care Practitioner Conference. Hilton Head Island, South Carolina. June 2007.
39. "Recognition and Treatment of Heart Failure in Pediatrics." Invited Lecture, Acute Care for the Primary Care Practitioner Conference. Hilton Head Island, South Carolina. June 2007.
40. "Neurodevelopmental Outcomes in Patients with Congenital Heart Disease." Invited Lecture, Acute Care for the Primary Care Practitioner Conference. Hilton Head Island, South Carolina. June 2007.
41. "Mental Health Issues in Patients with Muscular Dystrophy." The Irish American Paediatric Society Annual Meeting. Memphis, Tennessee. September 2007.
42. "Cardiac Transplantation." Pediatric Critical Care Medicine Noon Conference, Texas Children's Hospital. Houston, Texas. January 2008.
43. "Heart Failure." X Congresso Interamericano de Pediatria. Mexico City, Mexico. January 2008.

44. "Whatever Happened to My Adolescent Patient with Congenital Heart Disease: Transitioning to the Adult Cardiology Service." Invited Lecture, The 30th Annual Pediatric Postgraduate Symposium, Omni Hotel. Houston, Texas. April 2008.
45. "Cardiac Disease in Muscular Dystrophy." Invited Lecture, Muscular Dystrophy Association Meeting. Houston, Texas. April 2008.
46. "Update on Myocarditis in Children: Unanswered Questions." Invited Lecture, Scientific Basis of Heart Failure in Children Meeting. Estes Park, Colorado. May 2008.
47. "Novel Biomarkers in CHF." Invited Lecture, Cardiology 2009-12th Annual Update on Pediatric Cardiovascular Disease. Nassau, Bahamas. February 2009.
48. "Echocardiographic Findings in Children with Obstructive Sleep Apnea." Invited Lecture, Cardiology 2009-12th Annual Update on Pediatric Cardiovascular Disease. Nassau, Bahamas. February 2009.
49. "Hypertrophic Cardiomyopathy." Noon Conference, Texas Children's Hospital. Houston, Texas. February, 2009.
50. "Living with Congenital Heart Disease." Invited Lecture, Evening with Genetics, Natural Science Museum. Houston, Texas. February 2009.
51. "Chest Pain in the Pediatric Patient: When to be Concerned." Invited Lecture, Baylor College of Medicine Primary Care Pediatric Course, Hilton Oceanfront Resort. Hilton Head Island, South Carolina. June 2009.
52. "Recognition of Cardiovascular Disease in Pediatrics: Things Not to Miss." Invited Lecture, Baylor College of Medicine Primary Care Pediatric Course, Hilton Oceanfront Resort. Hilton Head Island, South Carolina. June 2009.
53. "Cardiovascular Findings in Williams Syndrome." Invited Lecture, National Williams Syndrome Conference. Houston, Texas. August 2009.
54. "Understanding the Variability in Noonan, Cardio-Facio-Cutaneous, and Costello Syndromes." Invited Lecture, Evening with Genetics, Natural Science Museum. Houston, Texas. September 2009.
55. "Steroids in Myocarditis." Invited Lecture, American Academy of Pediatrics, National Conference and Exhibition. Washington D.C. October 2009.
56. "Extracardiac Management of the ECLS Patient." ECMO Training Program, Texas Children's Hospital. Houston, Texas. November 2009.
57. "Outcome and Risk Stratification for Children with Left Ventricular Noncompaction: Findings from the Pediatric Cardiomyopathy Registry." Scientific Sessions, American Heart Association.

Orlando, Florida, November 2009.

58. "How to Find a Job." Fellows in Training Lecture Series, American College of Cardiology. Atlanta, Georgia. March 2010.
59. "The Cardiovascular, Genetic, and Therapeutic Implications of Muscular Dystrophy." Feigin Research Seminar, Texas Children's Hospital. Houston, Texas. March 2010.
60. "Cardiovascular Findings in Potocki-Lupski Syndrome." Plenary Session, American College of Medical Genetics. Albuquerque, New Mexico. March 2010.
61. "Aortic Disease in Pediatrics." Pediatric Congress of Guatemala. Guatemala City, Guatemala. April 2010.
62. "Cardiomyopathy Management in the Pediatric Intensive Care Unit." Pediatric Congress of Guatemala. Guatemala City, Guatemala. April 2010.
63. "Outcome and Risk Stratification for Children with Left Ventricular Noncompaction: Findings from the Pediatric Cardiomyopathy Registry." 2nd International Cardiomyopathy in Children Workshop. Bethesda, Maryland. May 2010.
64. "Left Ventricular Noncompaction: The Other Cardiomyopathy." Texas Heart Institute Grand Rounds, St. Luke's Episcopal Hospital. Houston, Texas. May 2010.
65. "Cardiomyopathy in Barth Syndrome." Barth Syndrome Foundation International Conference. Orlando, Florida. July 2010.
66. "Use of 2-D based strain for surveillance of chemotherapeutic induced cardiotoxicity in a pediatric population." Cancer and the Heart International Conference. Houston, Texas. November 2010.
67. "14 year old male with osteosarcoma." Cancer and the Heart International Conference. Houston, Texas. November 2010.
68. "Diagnosis and Management of Pediatric Heart Failure." Pediatric Grand Rounds, East Tennessee Children's Hospital. Knoxville, Tennessee. January 2011.
69. "Infections in Heart Failure." Division of Infectious Diseases Faculty Meeting, Cincinnati Children's Hospital Medical Center. Cincinnati, Ohio. January 2011.
70. "Chemotherapy-Induced Cardiotoxicity: Existing and Future Diagnostic and Therapeutic Strategies." Oncology Grand Rounds, Cincinnati Children's Hospital Medical Center. Cincinnati, Ohio. February 2011.
71. "Cardio Renal Syndrome: It's Time to Use Biomarkers." CRRT International Conference on Continuous Renal Replacement Therapies. San Diego, California. February 2011.

72. "Single Gene Disorders in Congenital Heart Disease." USCAP 2011 Annual Meeting, United States and Canadian Academy of Pathology. San Antonio, Texas. February 2011.
73. "How I Found the Right Mentor." ACC.11 American College of Cardiology, Career and Mentoring Session for Pediatric and Congenital Cardiologists. New Orleans, Louisiana. April 2011.
74. "Left Ventricular Cardiomyopathy: Current Diagnostic and Therapeutic Strategies." Heart Institute Grand Rounds, Cincinnati Children's Hospital Medical Center. Cincinnati, Ohio. April 2011.
75. "Heart Failure/VAD's." CICU Education Blitz 2011, Cincinnati Children's Hospital Medical Center. Cincinnati, Ohio. April 2011.
76. "Genetic Factors and Thoracic Aortic Disease." Thoracic aortic Disease Symposium, Bethesda North Hospital. Cincinnati, Ohio. April 2011.
77. "Genetically Triggered Aortopathies." Emerging Topics in Clinical Genomics Lecture Series, University of Cincinnati Genetic Counseling Graduate Program, Cincinnati Children's Hospital Medical Center. Cincinnati, Ohio. April 2011.
78. "Left Ventricular Noncompaction: The Other Cardiomyopathy." Grand Rounds, Henry Ford Health System. Detroit, Michigan. May 2011.
79. "The Genetics of Cardiomyopathy: From Bench to Bedside." Grand Rounds, Central Baptist Hospital. Lexington, Kentucky. July 2011.
80. "Heart Transplantation in Children." Heart Failure in Children Session, Fourth International Branislav "Brano" Radovancevic Heart Failure Forum. Belgrade, Serbia. September 2011.
81. "The Role of the Cardiovascular Genetics Service in the Heart Institute." Cincinnati Children's Hospital Medical Center, Grand Rounds. Cincinnati, Ohio. October 2011.
82. "The Heart & Genetics of the Heart." Team Taught Course for Graduate Students in Molecular & Developmental Biology and Disease Course Cincinnati Children's Hospital Medical Center. Cincinnati, Ohio. February 2012.
83. "The Cardiomyopathies-From Bench to Bedside." Pediatrics Grand Rounds, University of Kentucky. Lexington, Kentucky. February 2012.
84. "Career & Mentoring Session for Pediatric and Congenital Cardiologist Chair." ACC.12 61st Annual Scientific Session and Expo. Chicago, Illinois. March 2012.
85. "How I Found the Right Mentor." ACC.12 61st Annual Scientific Session and Expo. Chicago, Illinois. March 2012.
86. "Pediatric Heart Failure: Diagnosis and Management." Cincinnati Children's Hospital Medical Center, CICU Educational Blitz. Cincinnati, Ohio. April 2012.

87. "Transition of Congenital Heart Disease (CHD) Patients to Adulthood." 2012 Conference, Advances in the Management of Oncology, SCT, and Solid Organ Transplant Patients, OptumHealth Education. Scottsdale, Arizona. April 2012.
88. "Transition of Congenital Heart Disease (CHD) Patients to Adulthood." Cincinnati Children's Hospital Medical Center, Pediatric Cardiology Grand Rounds. Cincinnati, Ohio. May 2012.
89. "The Genetics of Cardiomyopathy Impacts on Clinical Practice." The Healthcare Accreditation Colloquium Webinar, August 2012.
90. "Diagnosis and Management of Heart Failure in the Pediatric Population." 2012 Cardiovascular Ultrasound Fall Conference, Cincinnati, Ohio, September 2012.
91. "Cardiorenal Syndromes – Heart Failure." 1st International Symposium on AKI in Children at the 7th Int'l Conference on Pediatric CRRT. Cincinnati, Ohio. September 2012.
92. "Cardiorenal Syndromes – Treatment Strategies for ADHF associated AKI." 1st International Symposium on AKI in Children at the 7th Int'l Conference on Pediatric CRRT. Cincinnati, Ohio. September 2012.
93. "Advanced Therapy for Heart Failure" Berlin Heart EXCOR® Pediatric Training Seminar, Cincinnati Children's Medical Center. Cincinnati, Ohio. October 2012.
94. "Long Term Support and Management." Berlin Heart EXCOR® Pediatric Training Seminar, Cincinnati Children's Medical Center. Cincinnati, Ohio. October 2012.
95. "Interactive Round Table Discussions and Case Presentations." Berlin Heart EXCOR® Pediatric Training Seminar, Cincinnati Children's Medical Center. Cincinnati, Ohio. October 2012.
96. "The Importance of Genetic Testing in Heart Failure and Rhythm Disturbances." Friday morning Cardiology Conference, Sharp Memorial Hospital. San Diego, California. October 2012.
97. "What Therapies Should We Be Stealing From Our Adult Colleagues." The Pediatric Cardiac Intensive Care Society. Miami, Florida. December 2012.
98. "Medical Management of End Stage Heart Failure." The Pediatric Cardiac Intensive Care Society. Miami, Florida. December 2012.
99. "Chronic Heart Failure Treatment in Children." 5th International Course on Pediatrics, Hospital Angeles Puebla, Hospital Angeles PHO and the State of Puebla College of Pediatrics. Puebla, Mexico. February 2013.
100. "Advanced Therapies for Heart Failure." 5th International Course on Pediatrics, Hospital

Angeles Puebla, Hospital Angeles PHO and the State of Puebla College of Pediatrics. Puebla, Mexico. February 2013.

101. "Etiologic Diagnosis of Cardiomyopathies." 5th International Course on Pediatrics, Hospital Angeles Puebla, Hospital Angeles PHO and the State of Puebla College of Pediatrics. Puebla, Mexico. February 2013.
102. "The Genetics of Cardiomyopathic Disease." Grand Rounds LSU Health New Orleans Health Sciences Center. New Orleans, Louisiana. February 2013.
103. "Myocarditis." PICU Fellow Lecture, Cincinnati Children's Hospital Medical Center. Cincinnati, Ohio. February 2013.
104. "Left Ventricular Noncompaction." Heart Institute Grand Rounds Presentation Cincinnati Children's Hospital Medical Center. Cincinnati, Ohio. May 2013.
105. "Restrictive Cardiomyopathy – To Transplant or Manage Medically, the Great Debate." Heart Failure/Transplant Educational Conference, Cincinnati Children's Hospital Medical Center. Cincinnati, Ohio. June 2013.
106. "Utilization of Genetic Testing in Clinical Practice." Colloquium Site Visit, The Children's Hospital of Philadelphia. Philadelphia, Pennsylvania. September 2013.
107. "Bridge to Transplant or Destination Therapy – Is there a better strategy." Heart Failure Society of America 17th Annual Scientific Meeting. Orlando, Florida. September 2013.
108. "Decongesting with Ultrafiltration." Pediatric Heart Failure Summit. Houston, Texas. October 2013.
109. "Early and Preventive Treatment of Heart Failure Associated with Neuromuscular Disorders." Scientific Session, American Heart Association. Dallas, Texas. November 2013.
110. "Cardio-Oncology: The Importance of the Heart in the Care of Cancer Patients." Faculty Research CrossTalk, Cincinnati Children's Hospital Medical Center. Cincinnati, Ohio. December 2013.
111. "Ruboxistaurin." THE CHOC Heart Institute, Congenital Cardiology Group (CCG) Innovation Summit 2014. Dana Point, California. January 2014.
112. "Genetic Causes of Cardiomyopathy." Arab Health Congress, 7th Middle East Pediatrics Conference. Dubai, UAE. January 2014.
113. "Advanced Therapy for Heart Failure Including Ventricular Assist Devices." Arab Health Congress, 6th Middle East Cardiovascular Disease and Intervention Conference. Dubai, UAE. January 2014.
114. "Evaluating the Severity of AS/AI; When to Consider Surgery." Arab Health Congress, 6th Middle East Cardiovascular Disease and Intervention Conference. Dubai, UAE. January 2014.

115. "Heart Failure/Cardiomyopathy." Dubai Health Care City (DHCC) Education Department. Dubai, UAE. January 2014.
116. "The Heart & Genetics of the Heart." Development and Disease Course, Cincinnati Children's Hospital Medical Center. Cincinnati, Ohio. February 2014.
117. "Cardiac Rehabilitation in Patients with Coronary Disease and Heart Failure." Cincinnati Clinical Exercise Testing and Therapeutics Symposium 2014, Cincinnati Children's Hospital Medical Center. Cincinnati, Ohio. March 2014.
118. "Heart Health and Ongoing Cardiac Surveillance for Cancer Survivors." CDBI Survivor Meeting, Cincinnati Children's Hospital Medical Center. Cincinnati, Ohio. May 2014.
119. "Heart Disease Secondary to Treatment of Childhood Cancer." CDBI Survivor Meeting, Cincinnati Children's Hospital Medical Center. Cincinnati, Ohio. May 2014.
120. "Pediatric/Adolescent HCM." HCMA Annual Meeting. Morristown Medical Center. Morristown, New Jersey. May 2014.
121. "HCM Mimickers - What Are Some of Them and Why are They Important." HCMA Annual Meeting. Morristown Medical Center. Morristown, New Jersey. May 2014.
122. "Pediatric/Adolescent HCM – How to Keep Them Active." HCMA Annual Meeting. Morristown Medical Center, Morristown, New Jersey. May 2014.
123. "Hypertrophic Cardiomyopathy in Pediatrics – Session: Management in 2014: When to Intervene." American Society of Echocardiography, 25th Annual Scientific Sessions. Portland, Oregon. June 2014.
124. "SciMed - Diagnosis and Management of Cardiovascular Disease in Barth Syndrome." Barth Syndrome Foundation Meeting. Clearwater, Florida. June 2014.
125. "Families Bridge Devices, Pharmaceutical Agents and Genetic Therapies." Barth Syndrome Foundation Meeting. Clearwater, Florida. June 2014.
126. "Pediatric Cardiomyopathy 101." Children's Cardiomyopathy Foundation, Inc. Webinar, September 2014.
127. "1P36 and the Heart." 2014 1p36 DSA Conference. Cincinnati, Ohio. July 2014.
128. "Heart Failure in Neuromuscular Disease." Pediatric Heart Failure Summit. Cincinnati, Ohio. September 2014.
129. "Types of Congenital Abnormalities and Surgical Interventions Leading to Heart Failure." Heart Failure Society of America 18th Annual Scientific Meeting. Las Vegas, Nevada. September 2014.

130. "The Fabry Heart." FSIG Expert Fabry Conference. Orlando, Florida. February 2015.
131. "Investigational new drug applications: The long and winding road." Cincinnati Children's Hospital Medical Center Heart Institute Research Retreat. Cincinnati, Ohio. September 2015.
132. "Treatment-Related Effect – Cardiac Problems." Essentials of Cancer Survivorship: A Workshop for Health Care Professionals. Midwest Consortium for Cancer Survivorship Education and Research. Cincinnati, Ohio. November 2015.
133. "Multidisciplinary Fabry Care: Challenges and Opportunities." The Power of Registries in Rare Disease: Expanding knowledge from birth to adulthood. 15th National Rare Disease Registries Meeting. Chicago, Illinois. November 2015.
134. "Is There a Role for VAD Destination Therapy in Children?" Innovations in Pediatric Heart Failure Symposium. San Diego, California. December 2015.
135. "Heart Failure in Neuromuscular Disease Patients." Innovations in Pediatric Heart Failure Symposium. San Diego, California. December 2015.
136. "Cardiac Function and Fibrosis and Cardiac MRI Endpoints for DMD Clinical Trials." BioMarin Pharmaceutical Advisory Board Meeting. San Rafael, California. February 2016.
137. "The Genetics of Cardiomyopathy." Cardiology 2016 – 19th Annual Update on Pediatric and Congenital Cardiovascular Disease. Orlando, Florida. February 2016.
138. "What Should I Do About My Patient With Non-compaction Type Cardiomyopathy?" Cardiology 2016 – 19th Annual Update on Pediatric and Congenital Cardiovascular Disease. Orlando, Florida. February 2016.
139. "Heart Transplantation for Congenital and Pediatric Cardiovascular Disease in 2016." Moderated Panel of Experts, Cardiology 2016 – 19th Annual Update on Pediatric and Congenital Cardiovascular Disease. Orlando, Florida. February 2016.
140. "Cardiovascular Implications of Cancer Treatment." UCCI Advanced Practice Providers about Treatment-Related Cardiovascular Problems. University of Cincinnati, Cincinnati, Ohio. April 2016.
141. "The Current and Future Landscape of Urinary Thromboxane Testing to Evaluate Atherothrombotic Risk." 2016 Ohio-Collaborative Laboratory Conference. Columbus, Ohio. April 2016.
142. "About Fabry Disease: A Silently Progressive, Increasingly Debilitating, Often Life-Threatening Disorder". Sanofi Genzyme Dinner Program. Phoenix, Arizona. May 2016
143. "Cardiac Effects of Cancer Treatment". St. Elizabeth Healthcare. Edgewood, Kentucky. May 2016

144. "Fabry Disease and the Heart – Early Cardiac MRI Findings and Rhythm Changes". North American Fabry Registry Advisory Board Meeting. Chicago, Illinois. June 2016.
145. "Cardiovascular Disease in Barth Syndrome: Diagnostic and Treatment Strategies". Barth Syndrome Foundation-8th International Scientific, Medical, and Family Conference. Clearwater, FL. July 2016.
146. "Taking Better Control of Fabry Disease: Importance of Regularly Scheduled Assessments". Genzyme Rare Disease 2016 U.S. Medical Roundtable, El Segundo, CA. August 2016.
147. Co-moderator, Genetics Scientific Education Program "Cardiology Focused Discussion Around Fabry Disease". Sanofi Genzyme US Medical Affairs, Rare Diseases. Los Angeles, CA. August 2016.
148. Moderator and "Home Monitoring in Heart Failure: Near or Remote?". 4th Pediatric Heart Failure Summit, The Hospital for Sick Children. Toronto, ON Canada. September 2016.
149. "Pediatric/Adolescent HCM". Hypertrophic Cardiomyopathy Association. Boston, MA. October 2016
150. "Initial Impressions of cMRI Imaging Studies at Month 6 Post Infusion". Capricor, DMD MRI Meeting, New Orleans, LA. November 2016
151. Panelist "Shock and Mechanical Support Simulation: Pediatric Heart Failure I". AHA Scientific Sessions 2016, New Orleans, LA. November 2016
152. "Fulminant Myocarditis in Children". AHA Scientific Sessions 2016, New Orleans, LA. November 2016
153. "Fabry Heart" FSIG Expert Fabry Conference, Cincinnati, OH. April 2017
154. "About Fabry Disease: A Silently Progressive, Increasingly Debilitating, Often Life-Threatening Disorder". Sanofi Genzyme Program. Boston Medical Center, Boston, MA. May 2017
155. "Targeting Protein Kinase C; A Novel Paradigm for Heart Failure Therapy". 4th International Conference on Cardiomyopathy in Children. Bethesda, MA. May 2017
156. "Taking Better Control of Fabry Disease: Importance of Regularly Scheduled Assessments". Sanofi Genzyme Dinner Program. Pittsford, NY. May 2017
157. "Left Ventricular Noncompaction: From Bench to Bedside". University of Iowa Grand Rounds. Cedar Rapids, IA. June 2017
158. "Cardiovascular Findings in Fabry Disease". Sanofi Genzyme WebEx / Medical College of Wisconsin. June 2017
159. "The Fabry Registry: N215S Mutation". 16th North American Rare Disease Registries Meeting 2017.

Chicago, IL. June 2017

160. "Acute – Chronic Pericarditis Etiologies and Management". 7th World Congress of Pediatric Cardiology and Cardiac Surgery, Dinner Meeting. Barcelona, Spain. July 2017
161. "Cardiac aspects of Barth syndrome". Barth Syndrome 9th International Scientific, Medical, and Family Conference. Clearwater, FL. July 2018.
162. "The Genetics of Cardiomyopathy: From Bench to Bedside". Preventive Medicine Grand Rounds, University of Tennessee, Memphis, TN. September 2018.
163. "Hypertrophic Cardiomyopathy in Children and Young Adults: Current Perspectives". Annual Mac Armour Memorial Lectureship, Le Bonheur Children's Hospital, Memphis, TN. October 2018.
164. "Left Ventricular Noncompaction: The Other Cardiomyopathy", Cariology Grand Rounds, University of Tennessee Health Science Center", Memphis, TN. October 2018.
165. "Hypertrophic Cardiomyopathy: Current Perspectives". J.M. Sullivan Distinguished Visiting Professor Lecture/Medicine Grand Rounds, University of Tennessee Health Science Center, Memphis, TN January 2019.
166. "Cardiovascular Findings in Fabry Disease: Early Cardiac MRI and Rhythm Changes". Cardiology Grand Rounds, Washington University, St Louis, MO, April 2019.
167. "Clinical Assessment and Management of Heart Failure". 3rd Annual Multispecialty Conference for the Primary Care Physician, FedEx Institute of Technology, Memphis, TN. March 2019.
168. "Hypertrophic Cardiomyopathy, Current Perspectives", Texas Heart Institute Grand Rounds, Houston, TX, May 2019
169. "Valvular and Aortic Involvement in Fabry Disease". 6th Update on Fabry Disease: Biomarkers, Progression, and Treatment Options, Prague, Czech Republic. May 2019.
170. "Cardiac-Renal Outcomes in Females Treated with Agalsidase Beta". The Rare Disease Registries, Chicago, IL. June 2019.
171. "Fabry Disease: Information for Patients, Families, and Friends" Fabry Patient Meeting, Minneapolis, MN, June 2019
172. "Fabry Disease, Cardiovascular Implications". Cardiology Grand Rounds, University of California Irvine, Irvine, CA, June 2019.
173. "Heritable Cardiovascular Disease". Cardiology Grand Rounds, University of Tennessee Health Science Center, Memphis, TN, August 2019.

174. "Cardiomyopathies I". Cardiomyopathy Lecture/Fellows Conference, Memphis, TN, September 2019
175. "Fabry Disease and the Heart". 9th Annual Fabry Family Education Conference, Greensboro, NC. September 2019
176. "Cardiomyopathies II". Cardiomyopathy Lecture/Fellows Conference. Memphis, TN, November 2019.
177. "Contemporary Cardiovascular Care". Methodist Healthcare Luncheon Talk. Peabody Hotel, Memphis, TN, November 2019.
178. "Recent Advances in Fabry Disease: Translating the Latest Science into Best Practice". Medicine Grand Rounds, University of Tennessee Health Science Center, Memphis, TN December 2019.
179. "Mentoring". GME Research Certification Program, University of Tennessee Health Science Center, Memphis, TN, February 2020.
180. "Developing Effective Research Collaborations". GME Research Certification Program, University of Tennessee Health Science Center, Memphis, TN, February 2020.
181. "Determining Effectiveness of Treatments on Cardiovascular Outcomes: Testing and Timing of Cardiac Assessments". 16th Annual WORLD Symposium, Orlando, FL, February 2020.
182. "Cardiology Updates". 4th Annual Multi-Specialty Conference for the Primary Care Physician, Memphis, TN, February 2020.
183. "Heritable Causes of Electrophysiologic Disease and the Role of Genetic Testing". Electrophysiology Grand Rounds, University of Tennessee Health Science Center, Memphis, TN, July 2020.
184. "Living With BTHS Cardiomyopathy". Speaker and Session Chairman, Barth Syndrome Foundation Visual Scientific and Medical symposium, July 2020.
185. "Genetically Triggered Cardiomyopathies". Cardiology Conference, University of Tennessee Health Science Center, Memphis, TN, October 2020.
186. "Ten Question Tuesday: Pulmonary Hypertension". Global Lecture, Memphis, TN, November 2020
187. "Cardiomyopathies". Cardiology Conference, University of Tennessee Health Science Center, Memphis, TN, November 2020.
188. "COVID 2021 Vaccinations: Concerns, Effectiveness. And Distributions". Corporate Exchange, Memphis, TN, January 2021.

189. "COVID-19 Treatments: The Road to Immunity". Direct Selling Education Foundation, Washington, DC, January 2021.
190. "Left Ventricular Noncompaction". 5th International Conference on Cardiomyopathy in Children, Buffalo, NY, March, 2021.
191. "Future Directions in Cardiomyopathies in Children". 5th International Conference on Cardiomyopathy in Children, Buffalo, NY, March, 2021.
192. Baylor Cardiology Group Sanofi Genzyme Fabry CJR. Virtual, April 2021.
193. "Unexplained Cardiac Manifestations – The case for Fabry". Sanofi Genzyme: National Peer to Peer Program Discussion. Virtual Event, May 2021.
194. "Enhancing the Diagnosis of Fabry Disease in Cardiology with Targeted Information: A Before-After Control-Impact Study" Fabry Cardiology CJR. Sanofi Genzyme. Virtual Event, June 2021.
195. "Enhancing the Diagnosis of Fabry Disease in Cardiology with Targeted Information: A Before-After Control-Impact Study". Cardiology Grand Rounds, University of Tennessee Health Science Center, Virtual Event, June 2021.
196. "Cardiovascular Findings in Fabry". FSIG Patient Meeting. Virtual Event, June 2021.
197. "Breaking the Cycle of Refractory Heart Failure". Nuwellis Webinar Series, June 2021.
198. "Treatment Landscape of Genetic Disease in Cardiology". Taiwan Society of Cardiology. Virtual Event, July 2021.
199. "In Your Practice: Recognizing and Treating Transthyretin Amyloid Cardiomyopathy (ATTR-CM)". Pfizer Speaking Event. Virtual Event, July 2021.
200. "Biomarkers". Cardio-Pulmonary Renal Working Group Meeting. Virtual Event, July 2021.
201. "Medical Management for Hereditary Cardiomyopathies". EducateNext 2021 Annual Education Training, Ambry Genetics, Virtual Meeting, September, 2021.
202. "Hypertrophic Cardiomyopathy". University of Tennessee Health Science Center Cardiology Fellowship Lecture Series. Memphis, TN, September, 2021.
203. "Fabry Disease". 16th Annual Cardiometabolic Health Congress, Washington, DC, October, 2021.

204. "HCM Challenges for Pediatric Cardiologists: Nomenclature, Syndromes, Management and Sudden Death Prevention...Is It a Different Disease in Children?". VII International HCM Summit. Virtual Event, October, 2021.
205. "Cardiovascular Research in the Midsouth". Clinical Trials Industry Advisory Committee. Memphis, Tennessee, November, 2021.
206. "Cardiovascular Findings in Fabry Disease". Grand Rounds. University of California-Irvine. Virtual event, November, 2021.
207. "Cardiac Wearables". Tennessee American College of Cardiology Annual Meeting. Nashville, Tennessee, November, 2021.
208. "Dilated Cardiomyopathy". University of Tennessee Health Science Center Cardiology Fellowship Lecture Series. Memphis, TN, November, 2021.
209. "Arrhythmogenic Cardiomyopathy". University of Tennessee Health Science Center Cardiology Fellowship Lecture Series. Memphis, TN, February, 2022.
210. "Restrictive Cardiomyopathy". University of Tennessee Health Science Center Cardiology Fellowship Lecture Series. Memphis, TN, March, 2022.
211. "Cardiovascular Findings in Fabry Disease". FSIG Fabry Expert Conference, Philadelphia, PA, April, 2022.
212. "Genetics of Arrhythmias". University of Tennessee Health Science Center Cardiology Fellowship Lecture Series. Memphis, TN, April, 2022.
213. "Remote Patient Monitoring". American College of Cardiology Tennessee Chapter Annual Meeting, Nashville, TN, November 2022.
214. "Best Practices for Using Blood Volume Analysis (BVA) to Reduce Heart Failure LOS, Readmissions, Mortality, and Costs". MedAxiom Webinar, November 2022.
215. "Heritable Cardiovascular Disease". Longden Seminar. University of Tennessee Health Science Center, Department of Physiology, January 2023.
216. "Defining Patient-Focused Outcomes in Fabry Disease". WORLD Symposium. Orlando, FL, February, 2023.
217. "Cardiovascular Findings in Fabry Disease". FSIG Expert Fabry Conference. Orlando, FL, February 2023.
218. "Fabry Male Concerns: Questions and Answers". FSIG Expert Fabry Conference. Orlando, FL, February 2023.

219. "A Focus on Cardiovascular Aspects of Fabry Disease in Women: Cardiovascular Implications of Rare Disorders: Lessons from Lysosomal Storage Disorders". University of California Irvine Medicine Grand Rounds. Irvine, California, March, 2023.
220. "Paving the Rough and Rigid Roads in LVNC and Restrictive Cardiomyopathy". Fouad Mobassaleh Symposium on Sudden Cardiac Death in the Young. Washington, DC, August 2023.
221. "Managing Cardiomyopathies in Lysosomal Disorders". Check Rare, Affinity CE, and LDTRC Quarterly Series on Lysosomal Disorders. Virtual Symposium. September 2023.
222. "Fabry Disease". American College of Cardiology Tennessee Chapter Annual Meeting, Nashville, TN, November 2023.
223. "A New Approach to Identifying Patients with Fabry Disease Using a Machine Learning Algorithm". Genetic Rare and Immune Disorders Symposium (GRIDS). Middleburg, Virginia, November 2023.
224. "Advancing Cardio-Oncology". Cardiology Oncology Innovation Network (COIN) Annual Meeting. Virtual Symposium. December 2023.
225. "Cardiovascular Findings in Fabry Disease". FSIG Fabry Expert Conference. San Diego, California, February 2024.
226. "Application of Artificial Intelligence in the Diagnosis of Fabry Disease". Fabry Disease Expert Summit, Tokyo, Japan, February 2024.
227. "Arrhythmia and Personalized Risk Stratification". 8th Update on Fabry Disease, Hamburg, Germany, June 2024.
228. "Blood Volume Analysis". University of Wisconsin- Madison Cardiology Grand Rounds. Madison, Wisconsin, July 2024.
229. "Cardiovascular Therapies in Barth Syndrome: Potential Opportunities on the Horizon". Barth Syndrome Foundation International Scientific, Medical, and Family Conference. Bonita Springs, Florida, August 2024.
230. "Advancing Collaboration in Patient Equity and Innovation in Fabry Disease Care". WORLD Symposium, San Diego, California, February 2025.

ABSTRACTS PRESENTED:

1. **Jefferies JL**, Keller BK, Wilson J, Noonan JA, Griffith C. Long term outcomes in patients with adult congenital heart disease. Abstracts, Fellow's Day Conference, Texas Children's Hospital, Houston, Texas. April 2002.
2. **Jefferies JL**, Dreyer WJ, Denfield SW, Price JF, Towbin JA. Initial use of nesiritide in a postoperative heart transplant patient with acute tubular necrosis and hyponatremia. Abstracts, International Pediatric Heart Failure Meeting, Houston, Texas. May 2004.
3. Price JF, Little K, Moffett BS, Towbin JA, Denfield SW, **Jefferies JL**, Clunie SK, Dreyer **WJ**. Plasma B-type natriuretic peptide levels in infants and children with chronic compensated and acute decompensated heart failure. Abstracts, 8th Annual Heart Failure Society of America Meeting, Toronto, Ontario. September 2004.
4. **Jefferies JL**, Belmont JW, Craigen WJ, Ware SM, Fernbach SD, Neish SR, Smith EO, Towbin JA. Genetic predictors and reverse remodeling of dilated cardiomyopathy in muscular dystrophy. Abstracts, American Academy of Pediatrics Meeting, San Francisco, California. October 2004.
5. **Jefferies JL**, Belmont JW, Craigen WJ, Ware SM, Fernbach SD, Neish SR, Smith EO, Towbin JA. Genetic predictors and reverse remodeling of dilated cardiomyopathy in muscular dystrophy. Abstracts, American Heart Association Scientific Sessions, New Orleans, Louisiana. November 2004.
6. **Jefferies JL**, Belmont JW, Craigen WJ, Ware SM, Fernbach SD, Neish SR, Smith EO, Towbin JA. Genetic predictors and reverse remodeling of dilated cardiomyopathy in muscular dystrophy. Abstracts, American Heart Association Scientific Sessions Online Continuing Medical Education, New Orleans, Louisiana. November 2004.
7. Dimas VV, Denfield SW, Cannon BC, Fenrich AL, Friedman RA, Smith EO, Clunie SK, Kim JJ, Price JF, **Jefferies JL**, Dreyer WJ, Kertesz NJ. Arrhythmias and sudden cardiac death in children with dilated cardiomyopathy. Abstracts, American Heart Association Scientific Sessions, New Orleans, Louisiana. November 2004.
8. Dimas VV, Kertesz NJ, Dreyer WJ, Kim JJ, **Jefferies JL**, Clunie SK, Cannon BC, Smith EO, Price JF, Denfield SW. Predictors of poor outcome in dilated cardiomyopathy, Abstracts, American Heart Association Scientific Sessions, New Orleans, Louisiana. November 2004.
9. Kim JJ, Dreyer WJ, Price SF, Clunie SK, Dimas VV, **Jefferies JL**, Rosenblatt H, Towbin JA, Denfield SW. Leukocyte suppression leads to improved clinical outcomes in children status-post orthotopic heart transplantation. Abstracts, American Heart Association Scientific Sessions, New Orleans, Louisiana. November 2004.
10. **Jefferies JL**, Kearney DL, Fraser CD, McKenzie ED, Mott R. Localization of dendritic cells and monocytes to the graft matrix of polytetrafluoroethylene grafts and in the palliation of cyanotic heart defects. Abstracts, American College of Cardiology Meeting, Orlando, Florida. March 2005.

11. **Jefferies JL**, Denfield SW, Dreyer WJ, Price JF, Kim JJ, Dimas VV, Clunie S, Smith EO, McMahon CJ, Wann TI, Moffett BS, Towbin JA. A prospective evaluation of intravenous nesiritide in pediatric heart failure. *Abstracts, American College of Cardiology Meeting*, Orlando, Florida. March 2005.
12. Tan LH, **Jefferies JL**, Denfield SW, Dreyer WJ, Mott AR, Dickerson HA, Price JF, Towbin JA, Ou CN, Chang AC. B-type natriuretic peptide predicts treatment outcomes in pediatric patients with decompensated heart failure in the intensive care setting. *Abstracts, American Heart Association Scientific Sessions*, Dallas, Texas. November 2005.
13. Moulik M, Breinholt JP, Dreyer WJ, Kearney DL, Price JF, Clunie S, Moffett BS, Kim **JJ**, **Jefferies JL**, Thomas A, Harbes BA, Bowles KA, Smith EO, Bowles NE, Denfield SW, Towbin JA. Viral endomyocardial infection is an independent predictor and potentially treatable risk factor for graft loss in pediatric cardiac transplant patients. *Abstracts, Fellow's Day Meeting*, Texas Children's Hospital, Houston, Texas. May 2006.
14. Moulik M, Breinholt JP, Dreyer WJ, Kearney DL, Price JF, Clunie S, Moffett BS, Kim **JJ**, **Jefferies JL**, Thomas A, Harbes BA, Bowles KA, Smith EO, Bowles NE, Denfield SW, Towbin JA. Viral endomyocardial infection is an independent predictor and potentially treatable risk factor for graft loss in pediatric cardiac transplant patients. *Abstracts, Young Investigators Competition, American Academy of Pediatrics*, Atlanta, Georgia. October 2006.
15. Rossano JW, Dreyer WJ, Kim JJ, Price JF, Clunie SK, Moulik M, Decker JA, Breinholt JP, McKenzie ED, Denfield SW, Towbin JA, **Jefferies JL**. Pre-Transplant Serum Creatinine Predicts Long-Term Outcome in Pediatric Heart Transplant Patients. *Abstracts, Second International Conference on Heart Failure in Children and Young Adults*, Dana Point, California. December 2006.
16. Decker JA, Dreyer WJ, Smith EO, Towbin JA, Price JF, **Jefferies JL**, Kim JJ, Clunie SK, Cannon BC, Denfield SW. Hypertrophic cardiomyopathy in children: Do adult risk factors for cardiac death apply? *Abstracts, American Heart Association Scientific Sessions*, Orlando, Florida. November 2007.
17. Rossano JW, Denfield SW, Smith EO, Kim JJ, Price JF, **Jefferies JL**, Decker JA, Clunie SK, Towbin JA, Dreyer WJ. B-type natriuretic peptide levels at greater than one year post-transplant predict graft survival in pediatric heart transplant patients. *Abstracts, American Heart Association Scientific Sessions*, Orlando, Florida. November 2007.
18. Rossano JW, Price JF, **Jefferies JL**, Mott AR, Heinle JS, Kim JJ, Dickerson HA, Ocampo EC, Dreyer WJ, Denfield SW, Towbin JA, Nelson DP, Morales DLS. Impact of extracorporeal life support, ventricular assist devices, and inotropes on survival while waiting for heart transplantation: An analysis of the United Network of Organ Sharing Database. *Abstracts, 7th International Symposium on Pediatric Cardiac Critical Care Sessions*, Miami, Florida. December 2008.
19. Dickerson HA, Moffett BS, Mott AR, **Jefferies JL**, Rossano JW, Price JF, Ocampo EC, Nelson DP. The etiology of adrenal dysfunction in critically ill pediatric patients with cardiac disease. *Abstracts, 7th International Symposium on Pediatric Cardiac Critical Care Sessions*, Miami, Florida.

December 2008.

20. Price JF, Pignatelli R, **Jefferies JL**, Kim JJ, Dreyer WJ, Denfield SW, Towbin JA. Heart failure symptoms and B-type natriuretic peptide concentrations in children with hypertrophic cardiomyopathy. *Abstracts, American Heart Association's Scientific Basis for Heart Failure in Children Conference*, Estes Park, Colorado. May 2008.
21. Rossano JW, Denfield SW, Smith EO, Kim JJ, Price JF, **Jefferies JL**, Decker JA, Clunie SK, Towbin JA, Dreyer WJ. Assessment of the Cylex ImmuKnow cell function assay in pediatric heart transplant patients. *International Society of Heart and Lung Transplantation Scientific Sessions*, Boston, Massachusetts. April 2008.
22. Brescia S, **Jefferies JL**, Rossano JW, Denfield SW, Price JF, Dreyer WJ, Towbin JA, Kim JJ. Fatal arrhythmias in pediatric left ventricular non-compaction. *Abstracts, American Heart Association Scientific Sessions*, New Orleans, Louisiana. November 2008.
23. Rossano JW, Morales DLS, Denfield SW, Zafar F, **Jefferies JL**, Kim JJ, Heinle JS, Towbin JA, Dreyer WJ. Impact of panel-reactive antibodies in long-term outcome in pediatric heart transplant patients: An analysis of the United Network of Organ Sharing Database. *Abstracts, International Society for Heart and Lung Transplantation, 29th Meeting and Scientific Sessions*, Palais des Congress, Paris, France. April 2009.
24. Rossano JW, Morales DLS, Zafar F, Goldstein SL, Smith EO, Denfield SW, Kim JJ, Price JF, Heinle JS, Dreyer WJ, **Jefferies JL**. Impact of kidney function on long-term survival in pediatric patients with end-stage heart failure undergoing heart transplantation: An analysis of the United Network of Organ Sharing Database. *Abstracts, 13th Annual Scientific Meeting, Heart Failure Society of America*, Boston, Massachusetts. September 2009.
25. Blinder JJ, Goldstein SL, Lee VV, Fraser CD, Nelson DP, **Jefferies JL**. A retrospective analysis of acute kidney injury in infants undergoing surgery for congenital heart disease. *Abstracts, Young Investigators Session, American Academy of Pediatrics National Conference and Exhibition*, Washington, D.C. October 2009.
26. Rossano JW, Zafar F, Graves DE, Dreyer WJ, Denfield SW, Kim JJ, Towbin JA, Decker JA, Heinle JS, **Jefferies JL**, Price JF, Bozkurt B, Morales DLS. Prevalence of heart failure related hospitalizations and risk factors for mortality in pediatric patients: An analysis of a nationwide sampling of hospital discharges. *Abstracts, American Heart Association Scientific Sessions*, Orlando, Florida. November 2009.
27. Pahl E, Canter CE, Colan SD, Lu M, Webber SA, Sleeper LA, **Jefferies JL**, Hsu DT, Everitt MD, Kantor PF, Kaufman BD, Wilkinson JD, Towbin JA, Lipshultz SE. Sudden death in 1803 children with dilated cardiomyopathy: Rates and risk factors. *Abstracts, American Heart Association Scientific Sessions*, Orlando, Florida. November 2009.
28. **Jefferies JL**, Colan SD, Sleeper LA, Towbin JA, Pahl E, Kantor PF, Everitt MD, Webber SA, Kaufman BD, Lamour JM, Canter CE, Hsu DT, Lipshultz SE. Outcome and risk stratification for

children with left ventricular noncompaction: Findings from the Pediatric Cardiomyopathy Registry. *Abstracts, American Heart Association Scientific Sessions*, Orlando, Florida. November 2009.

29. Molina KM, Denfield SW, Moulik M, Towbin JA, Price JF, **Jefferies JL**, Kim JJ, Dreyer WJ, Rossano JW. Viral endomyocardial infection in the 1st year post-transplant is associated with persistent inflammation in pediatric heart transplant patients. *Abstracts, American Heart Association Scientific Sessions*, Orlando, Florida. November 2009.
30. Wilmot I, McGarry MC, Morales DL, **Jefferies JL**. Mechanical circulatory support in the treatment of children with acute fulminant myocarditis: A single center 14-year experience. *American College of Cardiology Annual Scientific Sessions*. Washington, DC, April, 2010.
31. Towbin JA, Sleeper L, **Jefferies JL**, Colan SD, Webber SA, Canter CE, Hsu DT, Ware SM, Wilkinson JD, Orav J, Lipshultz SE. Genetic and viral genome analysis of childhood cardiomyopathy: The PCMR/PCSR experience. *American College of Cardiology Annual Scientific Sessions*. Washington, DC, April, 2010.
32. Riley AA, Blinder J, **Jefferies JL**, Bennett M, Devarajan P, Nelson DP, Goldstein SL. Effect of peritoneal dialysis on renal recovery in infants after congenital heart surgery. *Abstracts, 15th International Conference on Continuous Renal Replacement Therapy*. San Diego, California. February, 2010.
33. Alvarez JA, Orav EJ, Wilkinson JD, Lee DJ, Rusconi P, **Jefferies JL**, Hsu DT, Webber SA, Canter CE, Towbin JA, Sleeper LA, Cox GA, Lipshultz SE. Competing risk analysis of prognostic factors for death and transplant in pediatric dilated cardiomyopathy. *Abstracts, American Heart Association Council of Epidemiology Annual Meeting*, San Francisco, California. March 2010.
34. **Jefferies JL**, Martinez H, Pignatelli R, Furman P, Lupski J, Potocki L. Cardiovascular findings in Potocki-Lupski Syndrome (PTLS). *Abstracts, American College of Clinical Genetics*, Albuquerque, New Mexico, March 2010.
35. Maskatia S, Decker JA, Spinner JA, Kim, JJ, Price JF, **Jefferies JL**, Dreyer WJ, O'Brian Smith E, Rossano JW, Denfield SW. Restrictive Physiology Is Associated with Poor Outcomes in Children with Hypertrophic Cardiomyopathy. *Abstracts, American College of Cardiology ACC.11*, New Orleans, Louisiana. April 2011.
36. Walsh MA, **Jefferies JL**, Towbin JA, Czosek RJ. Conduction abnormalities in pediatric patients with restrictive cardiomyopathy. *Abstracts, American Heart Association Scientific Sessions*, Orlando, Florida, November, 2011.
37. Kantor P, Orav E, Wilkinson J, Webber S, Canter C, Colan SD, Towbin J, Everitt M, Pahl E, Ware S, Kaufman B, Rusconi P, Lamour J, **Jefferies JL**, Addonizio L, Lipshultz S, University of Miami, Miller School of Medicine, Miami, FL, USA Hospital for Sick Children, Toronto, Canada. Progressive Left Ventricular Changes Predict the Likelihood of Survival in Pediatric Dilated Cardiomyopathy: Findings From the Pediatric Cardiomyopathy Registry. *Abstracts, American College*

of Cardiology ACC.12, Chicago, Illinois. March 2012.

38. Michelle A. Grenier, Robert Hinton, Timothy, J. Knilans, **John L. Jefferies**, Wayne Mays, Nicholas Edwards, Jeffrey Towbin, Richard Czosek, Jeffery Anderson, Cincinnati Children's Hospital Medical Center, Cincinnati Ohio. *An Echo Screening Tool for Sudden Cardiac Death in Young Athletes*. ASE's 23rd Annual Scientific Sessions, 2012 American Society of Echocardiography (ASE) Scientific Sessions, National Harbor, Maryland. July 2012.
39. Pignatelli R., Srinivasan C., Xu A., **Jefferies JL.**, Ater, Joan. *Abnormal Myocardial Strain and Preserved Ejection Fraction in Children at Risk for Chemotherapy-related Cardiotoxicity*. ASE's 23rd Annual Scientific Sessions, 2012 American Society of Echocardiography (ASE) Scientific Sessions, National Harbor, Maryland. July 2012.
40. Kaddourah A, Goldstein SL, **Jefferies JL** *Kidney Injury Molecule-1 (KIM-1) is a Promising Urinary Biomarker to Detect Cardiorenal Syndrome in Children with Dilated Cardiomyopathy (DCM)*. Abstracts, American Heart Association Scientific Sessions, Los Angeles, California. November 2012.
41. Kaddourah A, Goldstein SL, Towbin JA, **Jefferies JL** *Prevalence, Outcome, and Predictors of Cardio-Renal Syndrome in Children with Dilated Cardiomyopathy*. Abstracts, American Heart Association Scientific Sessions, Los Angeles, California. November 2012.
42. Erin M Miller, MS, Richard Czosek, MD, Amy Garrison, MS, Paula Goldenberg, MD, Michelle Grenier, MD, **John L. Jefferies, MD**, Angela Lorts, MD, Ashley Parrott, MS, Jeffrey Towbin, MD, Stephanie M. Ware, MD, PhD, *Toward Evidence-Based Guidelines for Cardiac Screening in Pediatric Hypertrophic Cardiomyopathy*. The Heart Institute Retreat, Cincinnati Children's Hospital Medical Center.
43. Wong B, Hu S, Bange J, Miller L, Rybalsky I, Collins J, Boutwell D, Horn P, Rutter M, McCormick A, McGuire M, McMahon M, Sawnani H, **Jefferies J.** *Outcomes Associated with an Interdisciplinary Comprehensive Care Program for DMD Patients Treated with Long Term Glucocorticoids*. 17th International World Muscle Society's Congress, Perth, Australia. October 2012.
44. Tamara Thomas, MD, **John L. Jefferies, MS, MD**, Angela Lorts, MD, D. Woodrow Benson, MD, PhD, Jeffrey Anderson, MD, Kan Hor, MD, Zhiqian Gao, PhD, Linda Cripe, MD, Elaine Urbina, MS, MD. *Autonomic Dysfunction by Heart Rate Variability Analyses Correlates with Myocardial Fibrosis in Pediatric Duchenne Muscular Dystrophy*. American College of Cardiology Annual Scientific Sessions, San Francisco, California. March 2013.
45. **Jefferies JL.** Towbin JA, Ryan TD, Lucky A. *Cardiovascular findings in recessive dystrophic epidermolysis bullosa*. American College of Cardiology Annual Scientific Sessions, San Francisco, California. March 2013.
46. Morales DL, Zafar F, Lorts A, Ryan TD, Chin C, Towbin JA, **Jefferies JL.** *Worldwide Use of Syncardia Total Artificial Heart in Adolescents: A 25-Year Experience*. International Society for Heart and Lung Transplantation, 33rd Annual Meeting, Montreal, Quebec, Canada. April 2013.

47. Morales DL, Zafar F, Gaynor JW, Rossano JW, **Jefferies JL**, Ryan TD, Towbin JA, Lorts A. The Worldwide Use of Syncardia Total Artificial Heart in Patients With Congenital Heart Disease. International Society for Heart and Lung Transplantation, 33rd Annual Meeting, Montreal, Quebec, Canada. April 2013.
48. **John Jefferies**, James Brown, Wayne Mays, Christopher Stahl, Mark McDonald. Improved Resource Utilization and Patient Flow in an Outpatient Cardiomyopathy Clinic. QCOR 2013, Baltimore, Maryland. May 2013.
49. Kaddourah A, Uthup S, Madueme PC, Hooper DK, **Jefferies JL**, and Goebel J, *Aortopathy in Young Patients – Does it Improve After Kidney Transplantation?* International Pediatric Transplant Association (IPTA) 7th Congress on Pediatric Transplantation, Warsaw, Poland. July 2013.
50. Grenier Michelle, **Jefferies JL**, Chung Eugene, Menon Kailas, Hull Gregory, Westrich Jennifer, Menon Santosh G. *Effects of Strength and Aerobic Training (Rowing) on Cardiovascular Structure in Elite High School Athletes*. Heart Failure Society of America 17th Annual Scientific Meeting, Orlando, Florida. September 2013.
51. Morales David LS, Zafar Farhan, Wearden Peter D, Rosenthal David N, Cabrerra Antonio G, Rossano Joseph W, Humpl Tilman, **Jefferies JL**. *LVAD vs BiVAD use across the USA: Understanding when a particular device strategy is chosen and its effect on outcome*. CHSS Annual Meeting, Chicago, Illinois. October 2013.
52. Rossano W, **Jefferies JL**, Pah E, Naftel DC, Pruitt E, Lupton K, Dreyer WJ, Chinnock R, Boyle GJ, Mahle WT. *Use of Sirolimus in Pediatric Heart Transplant Patients: A Multi-institutional Study from the Pediatric Heart Transplant Study Group*. AHA Scientific Sessions 2013, Dallas, Texas. November 2013.
53. Bryant R, Zafar F, Castleberry C, Wilmot I, **Jefferies JL**, Chin C, Lorts A, Morales DL. *Post Transplant Survival Using the Berlin Heart Pediatric Ventricular Assist Device as a Bridge to Cardiac Transplantation*. American Heart Association Annual Scientific Sessions 2013, Dallas, Texas, November, 2013.
54. Kaddourah A, Goldstein SL, Bennet MR, Devarajan P, **Jefferies JL**. *The Time Is Now to Implement Novel Urinary Biomarkers to Identify Cardiorenal Syndrome in Children with Dilated Cardiomyopathy*. ASN Kidney Week 2013 Annual Meeting, Atlanta, Georgia. November 2013.
55. Ryan TD, **Jefferies JL**, Mehta P, Harris R, Bolyard A, Jones A, Shimamura A, Davies S, Myers S. *Echocardiographic Evaluation of Anatomy and Left Ventricular Systolic Function in Patients with Shwachman–Diamond Syndrome*. 7th International Congress on Shwachman-Diamond Syndrome. Toronto, Ontario. November 2013.
56. Tandon A, **Jefferies JL**, Hor KN, Wong BL, Ware SM, Mazur W, Fleck RJ, Gao Z, Sticka JJ, Benson DW, Taylor MD. *Dystrophin genotype-cardiac phenotype correlations in Duchenne and Becker muscular dystrophy using cardiac magnetic resonance imaging*. Eighth Annual Thomas Boat

Lectures, Cincinnati, Ohio. March 25, 2014. Cincinnati, Ohio. Platform presentation.

57. Tandon A, Taylor MD, Ware SM, **Jefferies JL**, Sticka JJ, Fleck RJ, Wong BL, Mazur W, Hor KN. *A longitudinal examination of cardiac dysfunction in patients with Duchenne and Becker muscular dystrophy via cardiac magnetic resonance imaging*. American College of Cardiology 62nd Annual Scientific Session, San Francisco, California. March 9, 2013. Moderated poster. (Poster abstract)
58. **Jefferies JL**, Towbin JA, Ryan T, Lucky A. *Cardiovascular Findings in Recessive Dystrophic Epidermolysis Bullosa*. American College of Cardiology 62nd Annual Scientific Session, San Francisco, California. March 9, 2013.
59. Thomas TO, **Jefferies JL**, Lorts A, Anderson J, Hor K, Gao Z, Urbina E. *Autonomic Dysfunction by Heart Rate Variability Analyses Correlates With Myocardial Fibrosis in Pediatric Duchenne Muscular Dystrophy*. American College of Cardiology 62nd Annual Scientific Session, San Francisco, California. March 9, 2013.
60. Tandon A, **Jefferies JL**, Hor KN, Wong BL, Ware SM, Mazur W, Fleck RJ, Gao Z, Sticka JJ, Benson DW, Taylor MD. *Dystrophin genotype-cardiac phenotype correlations in Duchenne and Becker muscular dystrophy using cardiac magnetic resonance imaging*. American College of Cardiology 63rd Annual Scientific Session, Washington, D.C., March 31, 2014. American College of Cardiology 2014 Young Investigator Awards Competition platform presentation.
61. Nandi D, Lin K, O'Connor M, Elci O, Kim JJ, Decker J, Price JF, Zafar F, Morales DL, Denfield SW, Dreyer WJ, **Jefferies JL**, Rossano JW. *Hospital charges for pediatric heart failure related hospitalizations admissions in the United States from 2000 to 2009*. American College of Cardiology 63rd Annual Scientific Session, Washington, D.C., March 31, 2014.
62. Kaddourah A, Goldstein SL, **Jefferies JL** *Kidney Injury Molecule-1 (KIM-1) Is the Best Urinary Biomarker to Detect Cardiorenal Syndrome In Children with Systolic Left Ventricular Dysfunction*. CRRT 2014, San Diego, California. March 2014.
63. Gerdes YM, Mays WA, Knecht SK, Wolfe MA, Schuckert LE, **Jefferies JL**, Towbin JA, Knilans TK. *Comparison Maximal Test Frequency Results to Exercise Test Modality in Cardiomyopathy Patients*. American College of Sports Medicine 61st Annual Meeting, Orlando, Florida. March 2014.
64. Zafar F, Chin C, Karani K, Lorts A, Wilmot I, **Jefferies JL**, Bryant III R, Ryan T, Towbin JA, Morales DS, Castleberry C. *Coronary Allograft Vasculopathy in Pediatric Heart Transplant: Is Re-transplant a prudent option for all*. ISHLT 34th Annual Meeting and Scientific Sessions, April 10-13, 2014 in San Diego, California.
65. Zafar F, Khan MS, Bryant III R, Castleberry C, Lorts A, Wilmot I, **Jefferies JL**, Chin C, Morales DL. *Pediatric heart transplant waitlist mortality in the era of ventricular assist devices*. ISHLT 34th Annual Meeting and Scientific Sessions, April 10-13, 2014 in San Diego, California.
66. Thomas T, Zafar F, Morales DS, Khan M, Chin C, Lorts A, **Jefferies JL**, Wilmot I, Castleberry C. *Allosensitization after Ventricular Assist Device does not impact post-transplant survival*. Poster

presentation, ISHLT 34th Annual Meeting and Scientific Sessions, April 10-13, 2014 in San Diego, California.

67. Khan MS, Alsaied T, Zafar F, Castleberry CD, Bryant III R, Wilmot I, **Jefferies JL**, Morales DLS. *Predictors of Long-Term Survival after Pediatric Heart Transplantation Change with Age*. ISHLT 34th Annual Meeting and Scientific Sessions, April 10-13, 2014, San Diego, California.
68. Parent JJ, Darragh R, Ryan TD, Lorts A, **Jefferies JL**, Towbin JA, Chin C. *Peri-Operative Cast Prevention for Pediatric Patients With Plastic Bronchitis Undergoing Heart Transplantation*. ISHLT 34th Annual Meeting and Scientific Sessions, April 10-13, 2014 in San Diego, California.
69. Parent JJ, Ryan TD, Castleberry C, **Jefferies JL**, Lorts A, Chin C. *Use of Bortezomib To Treat Antibody Mediated Rejection in a Patient Requiring Mechanical Circulatory Support After Heart Transplantation*. ISHLT 34th Annual Meeting and Scientific Sessions, April 10-13, 2014 in San Diego, California.
70. Shamszad P; Sower C, Ryan TD, Castleberry C, Lorts A, **Jefferies JL**, Wilmot I, Towbin JA, Chin C. *Cardiac Transplantation in Children with Chromosomal Anomalies: A Multi-Institutional Outcomes Analysis*. ISHLT 34th Annual Meeting and Scientific Sessions, April 10-13, 2014 in San Diego, California.
71. Puri K, Risma K, Kocoshis S, Chin C, Ryan T, **Jefferies JL**, Castleberry C. *T-Cell Mediated Inflammation Resulting in Multifocal Inflammatory Bowel Disease in a Pediatric Heart Transplant Patient*. ISHLT 34th Annual Meeting and Scientific Sessions, April 10-13, 2014 in San Diego, California.
72. Villa CR, Wilmot I, Castleberry C, Ryan TD, Del Corral M, **Jefferies JL**, Chin C, Morales DL, Lorts A. *Desensitization Utilizing Bortezomib and Plasmapheresis on a Patient Supported Via the Syncardia Freedom® Driver*. ISHLT 34th Annual Meeting and Scientific Sessions, April 10-13, 2014 in San Diego, California.
73. Villa CR, Zafar F, Castleberry C, Wilmot I, Ryan TD, **Jefferies JL**, Chin C, Morales DL, Lorts A. *Bridging Infants <5 kg: Should We Continue To Offer ECMO?* ISHLT 34th Annual Meeting and Scientific Sessions, April 10-13, 2014 in San Diego, California.
74. Zafar F, Castleberry C, Khan MS, **Jefferies JL**, Wilmot I, Clifford C, Ryan TD, Blitz A, Morales DL, Lorts A. *Allosensitization after Total Artificial Heart does not affect short-term survival* ASAIO 60th Annual Conference in Washington D.C., June 2014.
75. Lang S, Michelfelder E, Madueme P, Goldstein B, **Jefferies JL**, Ryan T. *3D Speckle Tracking-Derived E/SRe' Does not Correlate to Simultaneous Left Ventricular End-Diastolic Pressure Measurement in Children and Young Adults with Cardiomyopathy and Restrictive Physiology*. American Society of Echocardiography, 25th Annual Scientific Sessions. Portland, Oregon. June 2014.
76. Khan M, Zafar F, Bryant III R, Castleberry CD, Chin C, **Jefferies JL**, Morales DLS. *Does Simultaneous Abdominal Organ Harvesting Impact Cardiac Graft Survival In Children?*

World Transplant Congress, San Francisco, California. July 2014.

77. Zafar F, Khan M, Castleberry CD Yeager MR, Bryant III R, Horsley M, Chin C, **Jefferies JL**, Morales DLS. *Post-transplant Changes in Body Mass Index Affect Long-term Survival*. World Transplant Congress, San Francisco, California. July 2014.
78. Grenier M, Menon K, Menon S, Spar D, **Jefferies JL**, Hinton R, Volz B, Westrich J, Brown R, Coners D, Orman B, Chung E. *“Targeting the “Gray Area”: How Common Is Hypertrophy in the Elite High School Rower’s Heart*. Heart Failure Society of America 18th Annual Scientific Meeting, Las Vegas, Nevada. September 2014.
79. Parent JJ, Towbin JA, **Jefferies JL**. *Medical Therapy Leads to Positive Remodeling in Left Ventricular Non-Compaction Cardiomyopathy*. American Heart Association Scientific Sessions, Chicago, Illinois, November, 2014.
80. Ryan TD, Lucky AW, Towbin JA, **Jefferies JL**. Ventricular dysfunction and aortic dilation in patients with recessive dystrophic epidermolysis bullosa. American College of Cardiology Scientific Sessions, San Diego, California, March, 2015.
81. Castleberry C, Khan M, Shugh S, Wilmot I, Ryan TD, Chin C, **Jefferies JL**, Lorts A, Morales DL. *Determinates of Non-Utilization in Pediatric Heart Donors*. International Society for Heart and Lung Transplantation, 35th Annual Meeting and Scientific Sessions, Nice, France. April 2015.
82. Patel AR, Rossano JW, Kantor PF, Towbin JA, Colan SD, Everitt MD, **Jefferies JL**, Dodd DA, Silva JN, Janson CM, Wilkinson JD, LaRocca TJ, Lipshultz SE. *Eligibility for Cardiac Resynchronization Therapy for Systolic Heart Failure in Children with Cardiomyopathy*. International Society for Heart and Lung Transplantation, 35th Annual Meeting and Scientific Sessions, Nice, France. April 2015.
83. Mehmood M, Hor KN, Al-Khalidi H, Benson DW, **Jefferies JL**, Taylor MD, Egnaczyk GF, Raman SV, Basu S, Cripe L, Mazur M. *Comparison of Right and Left Ventricular Systolic Function Indices in Duchenne Muscular Dystrophy: A Longitudinal Cardiac Magnetic Resonance Study*. International Society for Heart and Lung Transplantation, 35th Annual Meeting and Scientific Sessions, Nice, France. April 2015.
84. Castleberry C, Taylor B, Hohlbein A, Ryan TD, **Jefferies JL**, Wilmot I, Lorts A, Chin C. *Conversion to Proliferation Signaling Inhibitors in Pediatric Heart Transplant Patients*. International Society for Heart and Lung Transplantation, 35th Annual Meeting and Scientific Sessions, Nice, France. April 2015.
85. O’Connor MJ, Wang N, Long J, Huang Y, Lin K, Singh T, **Jefferies JL**, Shaddy R, Rossano JW. *Variability in Cardiomyopathy Admissions and Transplant Volumes at US Children’s Hospitals*. Society for Heart and Lung Transplantation, 35th Annual Meeting and Scientific Sessions, Nice, France. April 2015.

86. Villa CR, Czosek RJ, Ahmed H, Khoury PR, Anderson JB, Knilans TK, **Jefferies JL**, Wong B, Spar D. *Utility of 24-Hour Holter Monitoring in Pediatric and Adolescent Patients with Duchenne Muscular Dystrophy*. PPMD 2015 Connect Care Conference, Washington D.C. June, 2015.
87. Starc JJ, Moore Ra, Villa Cr, **Jefferies JL**, Taylor MD. *Elevated Myocardial Extracellular Volume Fraction in Duchenne Muscular Dystrophy*. Cincinnati Children's Hospital Medical Center Heart Institute Research Retreat, Cincinnati, Ohio. September 2015.
88. Guerrier K, Madueme PC, **Jefferies JL**, Anderson JB, Spar DS, Knilans TK, Czosek RJ. *Unexpectedly Low ECG Voltage in Hypertrophic Cardiomyopathy Patients: Is Myocardial Fibrosis to Blame?* Cincinnati Children's Hospital Medical Center Heart Institute Research Retreat, Cincinnati, Ohio. September 2015.
89. Mathew J, Moore R, Spar D, Villa CR, Ryan T, Chin C, Bange J, Sawnani H, Taylor M, Wong B, **Jefferies JL**. *Myocardial Scar Burden Increases With Age And Is Associated With Decline In Left Ventricular Systolic Function In Becker Muscular Dystrophy*. Cincinnati Children's Hospital Medical Center Heart Institute Research Retreat, Cincinnati, Ohio. September 2015.
90. Wittekind S, **Jefferies JL**. *Cardiac Rehabilitations in Young Patients with Nonischemic Dilated Cardiomyopathy*. Cincinnati Children's Hospital Medical Center Heart Institute Research Retreat, Cincinnati, Ohio. September 2015.
91. Ware SM, Lipshultz SE, Colan SD, Shi L, Canter CE, Hsu D, Dodd DA, Everitt MD, Kantor PF, Addonizio LJ, **Jefferies JL**, Rossano J, Pahl E, Rusconi P, Schubert J, Lee T, Miller E, Tariq M, Wilkinson J, Towbin JA. *Genetic testing practices in pediatric cardiomyopathy: identifying opportunities to positively impact diagnosis and family-based risk stratification*. American Society of Human Genetics Meeting, Baltimore, Maryland. October 2015.
92. Mehmood M, Taylor MD, **Jefferies JL**, Raman SV, Ambach S, Mazur W. *Relationship of Right Ventricular Function and Respiratory Status in a Large Cohort of Duchenne Muscular Dystrophy*. Innovations in Pediatric Heart Failure Symposium, San Diego, California. December 2015.
93. Taylor M, Moore R, **Jefferies JL**, Gao Z, Starc J. *Elevated Myocardial Extracellular Volume Fraction in Duchenne Muscular Dystrophy*. SCMR 19th Annual Scientific Sessions, Los Angeles, California. January 2016.
94. Moore R, Taylor M, **Jefferies JL**, Mathew J, Starc J, Rattan M, Urbinelli L. *T1 Mapping in Becker Muscular Dystrophy Patients Detects Diffuse Microfibrosis Prior to Evidence of Late Gadolinium Enhancement or Cardiac Dysfunction*. SCMR 19th Annual Scientific Sessions, Los Angeles, California. January 2016.
95. Chung ES, Dadosky C, **Jefferies JL**, Egnaczyk GF, O'brien TM, Menon SG. *Optimisation of decongestion in acute decompensated heart failure: role of tolvaptan and aquapheresis*. Heart Failure 2016 and 3rd World Congress on Acute Heart Failure, Florence, Italy. May 2016. Moderated poster.

96. Lipshultz SE, Wilkinson JD, Shi L, Towbin JA, Canter CE, Hsu DT, Webber SA, Kantor PF, Everitt MD, Pahl E, **Jefferies JL**, Rossano J, Addonizio LJ, Dodd DA, Ware SM, Molina K, Colan SD; for the PCMR Study Group. *The cardiac biomarkers in children with cardiomyopathy multicenter study: Preliminary results for pediatric hypertrophic cardiomyopathy*. ACC.16 65th Annual Science Session & Expo, Chicago, Illinois. April 2016. Moderated poster. (Poster abstract).
97. Karani K, Mitsnefes M, Goldstein SL, **Jefferies JL**, Morales DL, Zafar F. *The burden of acute injury on children hospitalized with heart failure*. American College of Cardiology Annual Scientific Sessions, Chicago, Illinois, April, 2016.
98. Mathew J, Moore R, Spar D, Villa C, Bange J, Sawnani H, Taylor MD, Wong B, **Jefferies JL**. *Myocardial scar burden increases with age and is associated with decline in left ventricular systolic function in young patients with Becker muscular dystrophy*. American College of Cardiology Annual Scientific Sessions, Chicago, Illinois, April, 2016.
99. Lipshultz SE, Wilkinson JD, Shi L, Towbin JA, Canter CE, Hsu DT, Webber SA, Kantor PF, Everitt MD, Elfriede P, **Jefferies JL**, Rossano J, Addonizio LJ, Dodd DA, Ware SM, Molina K, Colan SD. *The Cardiac Biomarkers in Children with Cardiomyopathy Multicenter Study: Preliminary Results for Pediatric Hypertrophic Cardiomyopathy*. Pediatric Academic Societies Meeting, Baltimore, Maryland. May 2016.
100. Lipshultz SE, Wilkinson JD, Shi L, Towbin JA, Canter CE, Hsu DT, Webber SA, Kantor PF, Everitt MD, Elfriede P, **Jefferies JL**, Rossano J, Addonizio LJ, Dodd DA, Ware SM, Molina K, Colan SD. *The Cardiac Biomarkers in Children with Cardiomyopathy Multicenter Study: Preliminary Results for Pediatric Dilated Cardiomyopathy*. Pediatric Academic Societies Meeting, Baltimore, Maryland. May 2016.
101. **Jefferies JL**, Kudel I, Salbert L. *Correlates of Health-Related Quality of Life in Patients with Hypertrophic Cardiomyopathy*. Heart Failure Society of America, Orlando, Florida. September 2016.
102. Ryan TD, Parent JJ, Gao Z, Khoury PR, Dupont E, Smith JN, Wong B, Urbina EM, **Jefferies JL**. *Increased Arterial Stiffness is Present in Patients with Duchenne Muscular Dystrophy*. Heart Failure Society of America, Orlando, Florida. September 2016.
103. Wittekind SG, Mays W, Gerdes Y, Knecht S, Hambrook J, Border W, **Jefferies JL**. *Improved exercise performance in pediatric Fontan patients after cardiac rehabilitation*. American College of Cardiology Annual Scientific Sessions. Chicago, Illinois, April, 2017.
104. Wilmot I, Rodriguez M, Puri K, Feng J, Taylor B, Mathew J, Ryan TD, **Jefferies JL**. *Contemporary use of heart failure medications in pediatric patients with dilated cardiomyopathy*. American College of Cardiology Annual Scientific Sessions. Chicago, Illinois, April, 2017.
105. Ploutz M, Moore R, Ashiki M, Wisoyzkey B, Taylor B, Spurney C, Taylor MD, **Jefferies JL**. *Spironolactone therapy for cardiomyopathy in Duchenne muscular dystrophy*. American College of Cardiology Annual Scientific Sessions. Chicago, Illinois, April, 2017.

106. Ware SD, Colan SD, Wilkinson JD, Everitt MD, Towbin JA, Canter CE, **Jefferies JL**, Dodd DA. *The Genetic Architecture of Pediatric Cardiomyopathy*. American Society of Human Genetics Annual Meeting. Orlando, Florida. October 2017.
107. Lipshultz SE, Rossano JW, Shi L, **Jefferies JL**, , Colan SD, Pahl E, Everitt MD, Webber SA, Canter CE, Towbin JA, Kantor PF, Feingold B, Addonizio LJ, Lamour JM, Ware SM, Lee TM, Czachor JD, Razoky H, Wilkinson JD. *Cardiac Biomarkers Are Associated With Death and Listing for Heart Transplantation in Pediatric Patients With Newly Diagnosed Dilated Cardiomyopathy: A Multi-Center Study From the Pediatric Cardiomyopathy Registry*. American Heart Association Annual Scientific Sessions, Anaheim, California. November, 2017.
108. Kirmani S, Woodard PK, Shi L, Canter CE, Colan SD, Pahl E, Towbin JA, Webber SA, Rossano JW, Everitt MD, Molina KM, Kantor PF, **Jefferies JL**, Feingold B, Addonizio LJ, Ware SM, Chung WK, Ballweg JA, Lee TM, Razoky H, Czachor JD, Lunze F, Marcus E, Wilkinson JD, Lipshultz SE. *Are Echocardiogram and Magnetic Resonance Imaging (MRI) Comparable in Measuring Maximal Septal Thickness in Children With Hypertrophic Cardiomyopathy (HCM)?*. American Heart Association Annual Scientific Session, Anaheim, California. November, 2017.
109. **Jefferies JL**, Hopkin R. *Prevalence of Lymphedema in Andersen-Fabry Disease: A Report from the Fabry Registry*. American Heart Association Session, Anaheim, California. November, 2017.
110. Kirmani S, Woodard PK, Shi L, Canter CE, Colan SD, Pahl E, Towbin JA, Webber SA, Rossano JW, Everitt MD, Molina KM, Kantor PF, **Jefferies JL**, Feingold B, Addonizio LJ, Ware SM, Chung WK, Ballweg JA, Lee TM, Razoky H, Czachor JD, Lunze F, Marcus E, Wilkinson JD, Lipshultz SE. *Fibrosis and Hypertrophy Assessed by Magnetic Resonance Imaging (MRI) and Serum Biomarkers in Pediatric Hypertrophic Cardiomyopathy (HCM). A Report From the Pediatric Cardiomyopathy Registry*. American Heart Association Session, Anaheim, California. November, 2017.
111. Ware SM, Wilkinson JW, Tariq M, Shubert JA, Sridhar A, Colan SD, Shi L, Canter CE, Hsu DT, Webber SA, Dodd DA, Everitt MD, Kantor PF, Addonizio LJ, **Jefferies JL**, Rossano JW, Pahl E, Rusconi P, Chung WK, Towbin JA, Lal AK, Bhatnagar S, Anorow BJ, Dexheimer P, Martin LJ, Miller EM, Razoky H, Czachor JD, Lipshultz SE. *Exome Sequencing in a Pediatric Cardiomyopathy Cohort: Findings From the Pediatric Cardiomyopathy Registry*. American Heart Association Session, Anaheim, California. November, 2017.
112. Wittekind SG, Ryan TD, Gao Z, Zafar F, Chin CW, Hengehold TA, **Jefferies JL**. *Contemporary outcomes of pediatric restrictive cardiomyopathy with aggressive medical therapy*. American College of Cardiology Annual Scientific Sessions. Washington, DC, March, 2018.
113. Lipshultz SE, Rossano JW, Shi L, **Jefferies JL**, Colan SD, Pahl E, Everitt M, Webber SA, Canter CE, Towbin JA, Kantor P, Feingold B, Addonizio LJ, Lamour J, Ware S, Lee T, Czachor J, Razoky H, Wilkinson JD. *Cardiac biomarkers are associated with death and listing for heart transplantation in pediatric patients with newly diagnosed dilated cardiomyopathy: a multi-center study for the pediatric cardiomyopathy registry*. Pediatric Academic Society, Toronto, CA. May, 2018.

114. Lee T, Ware S, Miller E, Dexheimer P, Sridhar A, Lipshultz SE, Shi L, Wilkinson JD, Towbin JA, Webber S, Rossano JW, Hsu D, **Jefferies JL**, Lal A, Aronow B, Martin L, Razoky H, Czachor J, Chung W. *Revising clinical genetic panel test results for pediatric cardiomyopathy after exome sequencing*. Pediatric Academic Society, Toronto, CA. May, 2018.
115. Kirmani S, Woodard P, Canter CE, Shi L, Pahl E, Colan SD, Towbin JA, Ballweg J, Webber S, Wilkinson J, Rossano JW, Everitt M, Molina K, Kantor P, **Jefferies JL**, Feingold B, Addonizio L, Ware S, Chung W, Lee T, Czachor J, Razoky H, Lipshultz SE. *Fibrosis and hypertrophy assessed by magnetic resonance imaging (MRI) and serum biomarkers in pediatric hypertrophic cardiomyopathy (HCM). A report from the Pediatric Cardiomyopathy Registry Group*. Pediatric Academic Society, Toronto, CA. May, 2018.
116. Kirmani S, Woodard P, Shi L, Canter CE, Colan SD, Lunze F, Marcus E, Pahl E, Towbin JA, Ballweg J, Webber S, Wilkinson J, Rossano JW, Everitt M, Molina K, Kantor P, **Jefferies JL**, Feingold B, Addonizio L, Chung W, Ware S, Lee T, Razoky H, Czachor J, Lipshultz S. *Are echocardiogram and magnetic resonance imaging (MRI) comparable in measuring maximal septal thickness. A report from the Pediatric Cardiomyopathy Registry Group*. Pediatric Academic Society, Toronto, CA. May, 2018.
117. Martinez HR, Hengehold T, Taylor MD, Czosek RJ, **Jefferies JL**. *Cardiovascular findings in a contemporary cohort of patients with 1p36 deletion syndrome*. Heart Failure Society of America 22nd Annual Scientific Sessions, Nashville, TN. September, 2018.
118. Martinez HR, Ryan TD, Wilmot I, Casson P, Gao Z, Olberding NJ, **Jefferies JL**. *Assessment of soluble ST2 and BNP in pediatric patients with left ventricular dysfunction*. Heart Failure Society of America 22nd Annual Scientific Sessions, Nashville, TN. September, 2018.
119. Giri S, **Jefferies JL**, Thomas F, Davis RL, Akbilgic O. *Abnormalities within normal sinus rhythm*. QCOR American Heart Association Scientific Sessions, Arlington, VA. April, 2019.
120. Sapkota Y, Liu Q, Shelton, K, Wang X, Wilson CL, Wang Z, Mulorooney DM, **Jefferies JL**, Oeffinger KC, Morton LM, Zhang J, Armstrong GT, Bhatia S, Hudson MM, Robison LL, Yasui Y. *Genome-wide association study using whole-genome sequencing identifies a novel locus associated with increased risk of cardiomyopathy in adult survivors of childhood cancer: utility of a 2-stage analytic approach*. American Society of Clinical Oncology, Chicago, IL. May, 2019.
121. Patel M, **Jefferies JL**, McDonald M. *Intentional aortic bioprosthetic valve fracture to eliminate large paravalvular gaps with severe aortic regurgitation*. Transcatheter Cardiovascular Therapeutics Conference, San Francisco, CA. September, 2019.
122. **Jefferies JL**, Spar D, Chaouki AS, Casson P, Towbin JA, Czosek RJ. *Continuous versus intermittent arrhythmia monitoring in pediatric and adult patients with left ventricular noncompaction (LVNC)*. American heart Association scientific sessions, Philadelphia, PA, November, 2019.
123. Wallace E, Davis B, Wu J, Moynihan M, Griffin B, **Jefferies JL**, Keyzor I. *The Unmet Need in Fabry Disease: A Retrospective Analysis of Healthcare Claims in the United States Reveals*

Significant Burden of Illness. WORLD Symposium, Orlando, FL. February, 2020.

124. Dixon S, Lu L, Wilson CL, **Jefferies JL**, Merchant TE, Howell RM, Ness KK, Srivastava DK, Hudson MM, Robison LL, Chemaitilly W, Armstrong GT. *Prediabetes and progression to diabetes among adult survivors of childhood cancer in the St. Jude Lifetime Cohort*. American Society of Clinical Oncology Annual Meeting, May, 2020.
125. Lubas MM, Wang M, **Jefferies JL**, Ness KK, Ehrhardt MJ, Krull KR, Mulrooney DA, Srivastava DK, Robison LL, Hudson MM, Armstrong GT, Brinkman TM. *Emotional distress, stress, and cardiovascular health in adult survivors of childhood cancer*. American Society of Clinical Oncology Annual Meeting, May, 2020.
126. Gunturkun F, Davis RL, Armstrong GT, **Jefferies JL**, Ness KK, Green DM, Lucas JT, Srivastava DK, Hudson MM, Robison LL, Mulrooney DA, Soliman EZ, Karabayir I, Akbilgic O. *Deep learning for improved prediction of late-onset cardiomyopathy among childhood cancer survivors: A report from the St. Jude Lifetime Cohort (SJLIFE)*. American Society of Clinical Oncology Annual Meeting, May, 2020.
127. Sapkota Y, Qin N, Ehrhardt MJ, Wang Z, Wilson CL, Estep J, Rai P, Hankins JE, BurrIDGE P, **Jefferies JL**, Zhang J, Hudson MM, Robison LL, Armstrong GT, Mulrooney DA, Yasui Y. *Cardiomyopathy risk among childhood cancer survivors of African ancestry and its molecular mechanisms*. American Society of Clinical Oncology Annual Meeting, May, 2020.
128. Ortiz A, Mauer M, Ponce E, Yang M, Gudivada B, Hong GR, **Jefferies JL**. *Stabilization of kidney function decline and cardiomyopathy in male patients with classic Fabry disease: a pre- vs. post-agalsidase beta treatment Fabry Registry analysis*. 17th Annual WORLD Symposium, February, 2021.
129. **Jefferies JL**, Spencer AK, Warnock DG, Lau HA, Nelson MW, Giuliano JD, Zabinski JW, Boussios C, Curhan G, Bandaria JN, Gliklich RE. *Utilization of artificial intelligence to identify undiagnosed Fabry patients: development of a validated machine learning model*. 17th Annual WORLD Symposium, February, 2021.
130. Asbeutah AA, **Jefferies JL**. *Incidence of liver cirrhosis among patients with a Fontan circulation: A systematic review and meta-analysis*. American College of Cardiology Annual Scientific Sessions, Atlanta, Georgia, May, 2021.
131. Stamper J, Rawal A, **Jefferies JL**. *Single Center Aquapheresis Ultrafiltration Year One*. American College of Cardiology Annual Scientific Sessions, Atlanta, Georgia, May, 2021.
132. Mouksian K, Rawal A, Yedlapati N, Pullen D, **Jefferies JL**. *Amyloidosis – A Novel TTR Mutation in an Asian Female*. American College of Cardiology Annual Scientific Sessions, Atlanta, Georgia, May, 2021.

133. Wu NL, Chen Y, Math M, Dieffenbach BV, Li N, Ehrhardt MJ, Green DM, Hingorani S, Howell RM, **Jefferies JL**, Mulrooney DA, Oeffinger KC, Robison LL, Weil BR, Yuan Y, Yasui Y, Hudson MM, Leisenring WM, Armstrong GT, Chow EJ. *Development and validation of a prediction model for kidney failure in long-term survivors of childhood cancer*. American Society of Clinical Oncology Annual Meeting, Online, June, 2021.
134. Shah K, Khelli S, Delgado D, **Jefferies JL**, Towne M, Narayana A, Olugemo K. *Symptom burden and clinical characteristics of patients with mutations associated with hereditary transthyretin amyloidosis: Insights from referrals by cardiologists to a genetic testing programme*. European Society of Cardiology-Heart Failure Congress. Online, June, 2021.
135. **Jefferies JL**, Yaranov D, Silver M. *Volume-guided venous to venous ultrafiltration in hospitalized heart failure patients*. Heart Failure Society of America Annual Scientific Meetings. Denver, Colorado, September, 2021.
136. Patel M, Anderson K, Litzow J, Fink G, McDonald M, **Jefferies J**. *Same day discharge after TAVR, TEER, TMVR, Watchman device implantations: Call of the pandemic or expected evolution?* American College of Cardiology Quality Summit. Virtual. September, 2021.
137. Khella S, Shah K, Delgado D, Marti C, Keller A, **Jefferies JL**, Towne M, Gabriel A, Narayana A, Olugemo K. *Clinical characteristics of patients with transthyretin gene mutations in polyneuropathy manifestations of hereditary transthyretin amyloidosis*. American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM). Aurora, Colorado, October, 2021.
138. Asbeutah A, Salberg L, **Jefferies JL**. *Prevalence of depression and anxiety related symptoms among patients living with hypertrophic cardiomyopathy*. American Heart Association Annual Scientific Sessions, Boston, Massachusetts, November, 2021.
139. Yaranov D, Silver M, Thompson S, Strobeck J, **Jefferies JL**. *Blood volume analysis phenotypes in heart failure patient supported with left ventricular assist device*. American Heart Association Annual Scientific Sessions, Boston, Massachusetts, November, 2021.
140. Kayali S, Pour-Ghaz I, Heckle M, Ifedili I, Nance C, Kabra R, Jha SK, **Jefferies JL**, Levine YC. *Beyond ejection fraction: Novel clinical approaches towards sudden cardiac death risk stratification in patients with dilated cardiomyopathy*. Tulane University Southern Regional Meeting, New Orleans, Louisiana, February, 2022.
141. Gunturkun F, Mulrooney DA, Davis RL, Armstrong GT, **Jefferies JL**, Karabayir A, Yasui Y, Ehrhardt M, Srivastava K, Hudson M, Akbilgic O. *Artificial intelligence to predict late-onset cardiomyopathy among childhood cancer survivors using electrocardiogram, echocardiogram and clinical data*. Quality of Care and Outcomes Research Scientific Sessions, Reston, Virginia, May 2022.
142. Williams AM, Phillips N, Goodenough CG, Brinkman TM, Papini C, Jacola LM, Delaney A, Armstrong GT, **Jefferies J**, Khan RB, Robison LL, Hudson MM, Ness KK, Krull KR. *Neuropathy and neurocognitive impairment in long-term survivors of pediatric cancer treated without central*

nervous system (CNS) directed therapy. American Society of Clinical Oncology Annual Meeting, Chicago, Illinois, June, 2022.

143. Ehrhardt MJ, Liu Q, **Jefferies JL**, Mulrooney DA, Sapkota Y, Goldberg JF, Dixon SB, Lucas JT, Ness KK, Srivastava DK, Mazur M, Plana JC, Robison LL, Hudson MM, Yasui Y, Armstrong GT. *Associations between global longitudinal strain (GLS), N-terminal-prohormone brain natriuretic peptide (NT-proBNP) and subsequent cardiomyopathy (CM) in a clinically assessed cohort of childhood cancer survivors exposed to cardiotoxic therapy.* American Society of Clinical Oncology Annual Meeting, Chicago, Illinois, June, 2022.
144. Dixon SB, Wang F, Lu L, Wilson CL, **Jefferies JL**, Green DM, Merchant TE, Howell RM, Srivastava DK, Delaney A, Robison LL, Ness KK, Hudson MM, Chemaitilly W, Armstrong GT. *Prediabetes, progression to diabetes, and risk for late cardiovascular events and kidney disease among adult survivors of childhood cancer in the St. Jude Lifetime Cohort.* International Symposium on Late Complications after Childhood Cancer (ISLCCC) Annual Meeting, July 8-9 2022. Utrecht, Netherlands.
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ONLINE PUBLICATIONS, EDUCATION, AND ADVOCACY

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	U.S. Patent No. 12,042,489
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EXHIBIT B

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I. INTRODUCTION

1. I have been retained by Groombridge, Wu, Baughman & Stone LLP, counsel for Amicus Therapeutics US, LLC and Amicus Therapeutics, Inc. (collectively, “Amicus”) to provide expert testimony regarding the validity of certain claims of U.S. Patent Nos. 11,633,388 (“the ’388 Patent”), 12,042,489 (“the ’489 Patent”), 12,042,490 (“the ’490 Patent”), (together, the “Reassessment Patents”) and U.S. Patent No. 11,833,164 (“the ’164 Patent” or “Engineered Mutations Patent” and collectively with the Reassessment Patents, the “Asserted Patents”) in response to the opening expert report of Dr. Jeffrey A. Medin retained by defendants Aurobindo Pharma Ltd. and Aurobindo Pharma USA, Inc. (collectively, “Aurobindo”).

2. Dr. Medin provided opinions that (1) Claims 8 and 36 of the ’388 Patent, Claims 17 and 23 of the ’489 Patent, and Claim 9 of the ’490 Patent (collectively, the “Reassessment Patent Claims”) are obvious, and (2) Claims 23-27 of the ’164 Patent (the “Engineered Mutations Patent Claims”) and collectively with the Reassessment Patent Claims, the “Asserted Claims”) are obvious. I have been asked to respond to Dr. Medin’s invalidity opinions related to the Asserted Claims. I have also been asked to render opinions regarding what was well-understood, routine, and conventional regarding the Reassessment Patent Claims as of May 30, 2017, which I understand the parties agree is the priority date of the Reassessment Patent Claims, and what was well-understood, routine, and conventional regarding the Engineered Mutations Patent Claims as of August 7, 2019, which I understand the parties agree is the priority date of the Engineered Mutations Patent Claims.

3. My opinions are summarized below:

- **First**, it is my opinion that the Reassessment Patent Claims—Claims 8 and 36 of the ’388 Patent, Claims 17 and 23 of the ’489 Patent, and Claim 9 of the ’490 Patent—are not obvious. Specifically, it is my opinion that the prior art references that Dr. Medin analyzes, even when combined, fail to teach or disclose each element of the Reassessment Patent Claims. The differences between the inventions claimed in the Reassessment Patent Claims and the prior

art references that Dr. Medin relies on are such that the inventions would not have been obvious to a person of ordinary skill in the art as of May 30, 2017, which I understand the parties agree is the priority date of the Reassessment Patent Claims. Such a person also would have no motivation to combine the teachings of the prior art references to solve the issues addressed by the Reassessment Patent Claims. In addition, there was significant unpredictability in how Fabry patients with each of the mutations in the Reassessment Patent Claims would respond to migalastat. Lastly, in some instances the references even teach away from the inventions, such that a person of ordinary skill in the art would not have had a reasonable expectation of success in administering migalastat to Fabry patients with the mutations in the Reassessment Patent Claims. As such, Dr. Medin has failed to show that any of the Reassessment Patent Claims are obvious over the prior art combinations presented in Dr. Medin's opening report. Additionally, the strong evidence of objective indicia of nonobviousness indicates that the Reassessment Patent Claims would have been nonobvious to a person of ordinary skill in the art.

- **Second**, it is my opinion that the Engineered Mutations Patent Claims—Claims 23-27 of the '164 Patent—are not obvious. In particular, it is my opinion that the prior art references that Dr. Medin analyzes, even when combined, fail to teach or disclose each element of the Engineered Mutations Patent Claims. The differences between the inventions claimed in the Engineered Mutations Patent Claims and the prior art references that Dr. Medin relies on are such that the inventions would not have been obvious to a person of ordinary skill in the art as of August 7, 2019, which I understand the parties agree is the priority date of the Engineered Mutations Patent Claims. Such a person also would have no motivation to combine the teachings of the prior art references to solve the issues addressed by the Engineered Mutations Patent Claims. In addition, there was significant unpredictability in whether an unknown mutation would be associated with Fabry disease and how Fabry patients with each of the mutations in the Engineered Mutations Patent Claims would respond to migalastat. Lastly, a person of ordinary skill in the art would not have had a reasonable expectation of success in administering migalastat to Fabry patients with the mutations in the Engineered Mutations Patent Claims. As such, Dr. Medin has failed to show that any of the Engineered Mutations Patent Claims are obvious over the prior art combinations presented in Dr. Medin's opening report. Additionally, the strong evidence of objective indicia of nonobviousness indicates that the Engineered Mutations Patent Claims would have been nonobvious to a person of ordinary skill in the art.

- **Third**, it is my opinion that certain elements of the Reassessment Patent Claims and Engineered Mutations Patent Claims were not well-understood, routine, and conventional to a person of ordinary skill in the art as of the priority date of the Reassessment Patent Claims, that is May 30, 2017, and as of the priority date of the Engineered Mutations Patent Claims, that is August 7, 2019, respectively.

II. PROFESSIONAL BACKGROUND AND QUALIFICATIONS

4. My clinical practice and research focus on improving outcomes in genetic conditions by understanding their underlying causes. I have published on a range of disorders, from common to rare, including condition descriptions and genetic mechanisms. My research

has primarily involved lysosomal storage diseases and has included participating in clinical trials for enzyme replacement therapy (“ERT”), oral chaperone drugs, and gene therapy. I am also interested in repurposing existing medications for rare genetic syndromes, such as mitogen-activated protein kinase (“MEK”) inhibitors for neurofibromatosis type 1.

5. Throughout my career, I have been honored with numerous awards that reflect both my commitment to patient care and education, and my dedication to research. For example, in 1994, I received the Outstanding Medical Research Award during my pediatric residency. In 2001, I was named Teacher of the Year at Cincinnati Children’s Hospital Medical Center (“CCHMC”). I received the Fabry Physician Award from the Fabry Support and Information Group in 2016, was nominated for the Research, Advocacy, Resources, and Education (“RARE”) Champion of Hope in Medical Care & Treatment in 2017, and received the Award of Appreciation from the National Fabry Disease Foundation in 2018. I was named one of Cincinnati’s “Top Docs” in Genetics multiple years between 2014 and 2021. In 2021, I received both the CCHMC Hidden Gems Award and the Outstanding Research Team Award as part of the Neurofibromatosis Team.

6. I earned a Bachelor of Science degree in zoology at Brigham Young University in Provo, Utah in 1986. I then pursued my medical degree at the University of Nevada School of Medicine in Reno, Nevada graduating with my M.D. in 1990. Following medical school, I completed my pediatric residency from 1990 to 1993 at Phoenix Children’s Hospital and Maricopa Medical Center in Phoenix, Arizona. I stayed on for an additional year, serving as chief resident from 1993 to 1994. Subsequently, I specialized in genetics by completing a fellowship in human genetics at the CCHMC, from 1994 to 1997.

7. My academic career began in 1997 as an instructor of Clinical Pediatrics in the Division of Human Genetics at both CCHMC and the University of Cincinnati College of Medicine's Department of Pediatrics. I held this position until 2000. In July 2000, I was appointed Assistant Professor of Clinical Pediatrics in the same division at both institutions, serving in that capacity until June 2008. From 2002 to 2008, I also held a concurrent appointment as an Assistant Professor in the Department of Analytical & Diagnostic Sciences within the College of Allied Health Sciences at the University of Cincinnati. In 2008, I was promoted to Associate Professor of Clinical Pediatrics in the Division of Human Genetics at CCHMC and the University of Cincinnati College of Medicine, a position I held until October 2022. Additionally, I served as Associate Professor in the Department of Analytical & Diagnostic Sciences at the University of Cincinnati from 2008 to 2011. In 2022, I was promoted to Professor of Clinical Pediatrics in the Division of Human Genetics at both CCHMC and the University of Cincinnati College of Medicine, where I currently serve.

8. Since 1993, I have published more than 230 book chapters and articles in prestigious journals such as American Journal of Medical Genetics, Annals of Neurology, Neurology, Pediatrics, Human Mutation, Nature Genetics, American Journal of Cardiology, Human Genetics, Hepatology, Science Advances, Neuron, Pediatrics, Lancet Neurology, and Journal of Hepatology. Several of these publications are related to research in the areas of pediatrics, genetics, lysosomal storage diseases, and neurology. I have also contributed to important studies regarding the management of Fabry disease in children and adults. I have also contributed to more than 300 abstracts presented at national and international symposia.

9. Throughout my career, I have been actively involved in diverse research projects that are related to genetics education, clinical trials, and therapeutic development for rare genetic

disorders. My early research was supported by grants from the National Institutes of Health and the National Center for Human Genome Research from 1999 to 2003. I served as co-investigator for these projects that focused on providing a genetics educational program for the nursing faculty. These projects aimed to enhance genetics education among nursing faculty nationwide and had a lasting impact on training programs. I contributed to securing a competitive renewal grant that significantly expanded the program's scope. The renewal increased funding and commitment to the development and dissemination of innovative, clinically relevant genetics curricula. This program remained active for over a decade.

10. In parallel, from 2000 to 2001, I contributed to a project that focused on genetics in primary care that was funded by the Health Resources and Services Administration ("HRSA"). This project focused on genetics faculty development for primary care providers. As a co-investigator, I supported the development of educational tools and strategies to integrate genetics into everyday clinical practice for physicians in family medicine, internal medicine, and pediatrics.

11. I have served as a principal investigator ("PI") for multiple industry-sponsored studies that span a wide range of technologies, from ERT, enzyme inhibitors, pharmacological chaperones, and gene therapy. These studies are summarized below.

A. ERT

12. ERT is a type of treatment that provides a patient with a recombinant enzyme when the patient's endogenous enzyme—such as human alpha-galactosidase A ("α-Gal A"), which facilitates the breakdown various molecules in the lysosome, including globotriaosylceramide (Gb3), which accumulates in Fabry disease (discussed in more detail below)—is missing or defective. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

13. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

B. Pharmacological Chaperones

14. A pharmacological chaperone is a type of molecule that influences the folding, structure, and/or stability of a specific target protein, such as α -Gal A. I was a PI for Amicus's ASPIRE study, as well as a PI for its long-term extension study, which evaluates the safety and efficacy of the pharmacological chaperone, Galafold®, in pediatric Fabry patients with amenable mutations. All of my enrolled participants continued from the first part of the study into the extension phase, which is ongoing. In addition to participating in Amicus's ASPIRE study and its extension study, I also treat approximately 29 patients with Galafold® as a part of my clinical practice. These patients have 11 different amenable mutations. One of these mutations, L89F, is one of the specific α -GAL A mutations listed in Claims 17 and 23 of the '489 Patent.

C. Enzyme Inhibitors

15. Enzyme inhibitors comprise a class of molecules that block the activity of an enzyme, such as glucosylceramide synthase, which catalyzes the synthesis of glucosylceramide, a precursor to Gb3. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

D. Gene Therapy

16. Gene therapy refers to providing a functional copy of a gene to a patient that has a defective gene, such as the gene for α -Gal A, sometimes called “GLA.” I have been actively engaged in gene therapy research for lysosomal storage disorders, including Fabry disease. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

17. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

18. Attached hereto as **Exhibit 1** is my curriculum vitae further describing my background and experience.

III. COMPENSATION AND PRIOR TESTIMONY

19. For my work on this matter, I am being compensated at a rate of \$500 per hour, which is my standard rate except for providing testimony at deposition and trial. For time spent testifying at deposition or at trial, I am being compensated at a rate of \$750 per hour, which is my standard rate. My rate is not contingent on the opinions set forth in this report or on the outcome of the litigation.

20. In the last four years, I have not provided testimony as an expert at any trials or depositions.

IV. DOCUMENTS AND MATERIALS REVIEWED

21. My opinions are based on my own knowledge and experience as well as on numerous documents that I have reviewed and considered, which are listed in **Exhibit 2**.

V. GENERAL LEGAL PRINCIPLES

22. As an initial matter, I am not an attorney, but counsel for Plaintiffs have explained certain legal principles relevant to my work in this matter to aid my analysis. I have applied those legal principles to my analysis described in this report.

A. Presumption of Validity

23. I have been informed that issued patents are presumed to be valid. I have been informed that to rebut this presumption the challenger, in this case, Aurobindo, must persuade a fact finder, such as a judge, by clear and convincing evidence that the patent claims are not valid. I have also been informed that clear and convincing evidence means that it is highly and substantially more likely to be true than untrue and that the fact finder must be convinced that the contention is highly probable.

B. Claim Construction

24. I have been informed that the terms of the patent claims are given the meaning they would have had to a person of ordinary skill in the art at the time of the invention. I understand that the claim terms are read in the context of the claim in which they appear, including in the context of all of the claims, and the entire patent specification, as well as the prosecution history.

25. I have been informed that the time of the invention (also known as priority date) of the Reassessment Patent Claims is May 30, 2017. I have also been informed that the time of the invention of the Engineered Mutations Patent Claims is August 7, 2019. I understand that Aurobindo does not dispute these two dates, nor does Dr. Medin provide any opinion that the Reassessment Patent Claims are not entitled to a May 30, 2017 priority date or that the Engineered Mutations Patent Claims are not entitled to an August 7, 2019 priority date. If Aurobindo contests the priority dates of either the Reassessment Patent Claims or the Engineered Mutations Patent Claims in the future, I reserve the right to address the priority dates in response to such opinion.

26. I have been informed that the parties have agreed on the meaning of the claim term **“HEK assay amenable mutation,”** which appears in each of the Reassessment Patent Claims. I have been informed that the agreed-upon meaning of “HEK assay amenable mutation” is “mutant form of α -galactosidase A (“ α -Gal A”) showing a relative increase of ≥ 1.2 -fold over baseline and an absolute increase of $\geq 3.0\%$ wild-type α -GAL A activity in the presence of 10 $\mu\text{mol/l}$ migalastat determined using the Good Laboratory Practice (‘GLP’)-validated HEK assay.” In forming my opinions, I have applied this construction to the Reassessment Patent Claims.

27. For all other claim terms, I have applied their plain and ordinary meaning.

C. Person of Ordinary Skill in the Art

28. I have been informed that the scope of the claim terms and whether a product infringes the claim are assessed from the standpoint of a person of ordinary skill in the art at the time of the invention. As discussed above, I have been informed that the time frame for assessing the Reassessment Patent Claims is the priority date, May 30, 2017, and that the relevant time frame for assessing the Engineered Mutations Patent Claims is the priority date, August 7, 2019.

29. I understand that Amicus proposed the following definition of a person of ordinary skill in the art for the Reassessment Patents and the Engineered Mutations Patent:

An individual with a degree in biology, pharmacology, medicine, or a related discipline with one to two years of experience in Fabry disease. Such a person of ordinary skill may also work as part of a multi-disciplinary team and draw upon not only his or her own skills but also take advantage of certain specialized skills of others on the team to solve a given problem.

I agree with this definition and adopt it for my analysis.

30. Based on my background and professional experience, by 2017 (for the Reassessment Patent Claims) and by 2019 (for the Engineered Mutations Patent Claims), I was at least a person of ordinary skill in the art.

31. I understand that Dr. Medin has offered¹ the following alternative definition of the person of ordinary skill:

a POSA to whom the '388, '489, '490, and '164 patents are directed, and given the seriousness of the potential health risks associated with administering pharmaceutical agents, suggests that one of ordinary skill in the field of pharmaceutical research and development would have a fairly high level of education and skill. Such skilled artisans would be those familiar with the field of metabolic disorders such as Fabry disease and would include pharmaceutical chemists or physicians involved in research and development of formulations for treatment of such disorders, who would have a Master's, Ph.D., and/or M.D.

¹ Medin Opening Report, ¶ 30.

degree and several years of experience in the field. The amount of experience in the field would depend upon the level of formal education and particular experience with drugs for the treatment of Fabry disease. A POSA would have worked in conjunction with other individuals, the group of which collectively would have had experience in these fields, as well as in the field of clinical development of drugs for the treatment of Fabry disease patients having renal impairment. A POSA would also have knowledge of the scientific literature concerning these fields as of the claimed priority dates of the asserted patents. A POSA may also work as part of a multidisciplinary team and draw upon not only his or her own skills but also take advantage of certain specialized skills of others in the team to solve a given problem.

32. I disagree with Dr. Medin's definition because it is too restrictive. For example, a physician does not have to be involved in research and development of formulation for treatment of Fabry to be considered a person of ordinary skill in the art.

33. My opinions remain the same, even under the definition of a person of ordinary skill proposed by Dr. Medin.

D. Nonobviousness

34. I have been informed that a patent is not valid if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time of the priority date of the invention to a person having ordinary skill in the art to which said subject matter pertains. As discussed above, I understand that the relevant time frame for the Reassessment Patent Claims is their priority date, May 30, 2017, and that the relevant time frame for the Engineered Mutations Patent Claims is their priority date, August 7, 2019. Dr. Medin does not provide any opinion that the Reassessment Patent Claims are not entitled to a May 30, 2017 priority date or that the Engineered Mutations Patent Claims are not entitled to an August 7, 2019 priority date. If Aurobindo contests the priority dates of either the Reassessment Patent Claims or the Engineered Mutations Patent Claims in the future, I reserve the right to address the priority dates in response to such opinion.

35. It has been further explained to me that, to determine whether the subject matter would have been obvious, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. I have also been informed that, even if a combination of prior art references discloses all of the limitations of the asserted claims, a patent challenger needs to offer clear and convincing evidence indicating why a person having ordinary skill in the art would have looked to those references, would have been motivated to combine the references at the time of the invention, and would have arrived at the claimed invention with a reasonable expectation of its successful implementation at the time of the invention.

36. Further, I have been informed that in analyzing whether the subject matter would have been obvious, one may consider whether there are a finite number of identified, predictable solutions to choose from with a reasonable expectation of success. For this analysis, counsel have explained to me that one should consider certain factors including the characteristics of the science or technology, its state of advance, the nature of the known choices, the specificity of the prior art, and the predictability of results in the area of interest. Further, it has been explained to me that varying all parameters or trying each one of numerous possible choices until one trial gives a successful result when prior art references do not give any indication of which parameters were necessary or no direction on how many potential choices would be successful does not mean that something was obvious to try.

37. I have also been informed that objective evidence of nonobviousness should be considered in determining whether the claimed subject matter would have been obvious. These indicia include whether there was a long-felt but unmet need that was satisfied by the claimed invention; whether others tried but failed to solve the problem solved by the claimed invention;

whether there has been industry praise of the claimed invention; whether the claimed invention achieved unexpectedly superior results over the closest prior art; whether products covered by the claimed invention have been commercially successful due to the claimed invention; whether experts were skeptical that the invention would work; the teaching away from the claimed invention by others; and whether others copied the claimed invention.

38. I have been informed that evidence of each of these objective indicia is relevant only if a nexus, i.e., a connection, exists between the evidence of the objective indicia and the product's characteristics that embody that claimed invention.

39. I have been further informed that although the patent holder may come forward with such objective evidence, the patent holder has no obligation to do so.

E. Patent Eligibility

40. I have been informed that patents grant a monopoly to those who invent or discover a new and useful, process, machine, manufacture, or composition of matter under 35 U.S.C. § 101. Counsel have explained to me that laws of nature, natural phenomena, and abstract ideas are not patentable because they are considered to be the basic tools of scientific and technological work.

41. Counsel have also explained that to determine if a patent is valid under 35 U.S.C. § 101, courts must first decide whether the claims at issue are directed to laws of nature, natural phenomena, or abstract ideas. Counsel have informed me that if the claims are not directed to laws of nature, natural phenomena, or abstract ideas, then they are patent eligible. Counsel have also informed me that if the claims are directed to laws of nature, natural phenomena, or abstract ideas, then courts must consider the elements of each claim both individually and as an ordered combination to determine whether there is an inventive concept in the claim that transforms the nature of the claim into a patent-eligible application of such laws of nature, natural phenomena,

or abstract ideas. I have been informed that even if a patent is directed to a law of nature, a natural phenomenon, or an abstract idea, an inventive concept can be found in the non-conventional and non-generic arrangement of known and conventional pieces.

42. Counsel have further explained that the question of whether an inventive concept transforms the nature of the claim into a patent-eligible application may be informed by whether the elements of a claim were well-understood, routine, and conventional. It has been explained to me that whether something is well-understood, routine, and conventional to a skilled artisan as of the priority dates (May 30, 2017 for the Reassessment Patent Claims and August 7, 2019 for the Engineered Mutations Patent Claims) goes beyond what was simply known in the prior art, and that the mere fact that something is disclosed in a piece of prior art does not mean it was well-understood, routine, and conventional.

VI. BACKGROUND OF THE TECHNOLOGY

A. A Rare Lysosomal Storage Disease: Fabry Disease

43. Lysosomal storage diseases “(LSDs”) are heritable metabolic diseases that affect the function of the lysosome.² The lysosome is a specialized organelle within cells that perform essential functions.³ Within the lysosomes, specialized enzymes degrade and reuse cellular lipids and biomolecules.⁴ When these enzymes are deficient, cells accumulate cellular debris

² Platt, F.M., (2018) Lysosomal Storage Diseases, *Nat rev Dis Primers* **4**(1):27 (ATGAL_10161649 at -649).

³ See, e.g., Germain 2012, D., (2010) Fabry Disease, *Orphanet J. of Rare Dis.* **5**:30 (ATGAL_10034456 at -456–57).

⁴ See Sun, A., (2018) Lysosomal Storage Disease Overview, *Ann. Transl. Med.* **6**(24):476 (ATGAL_10161327 at -327); Gros, F., Muller, S., (2023) The Role of Lysosomes in Metabolic & Autoimmune Diseases, *Nature Revs. Nephrology* **19**:366–83 (ATGAL_10161508 at -509, -513, -521); Platt, F.M., (2018) Lysosomal Storage Diseases, *Nat rev Dis Primers* **4**(1):27 (ATGAL_10161649 at -649).

that may lead to metabolic diseases and disorders also known as LSDs.⁵ These disorders are caused by mutations in genes encoding lysosomal proteins, such as lysosomal glycosidases, proteases, integral membrane proteins, transporters, enzyme modifiers or activators.⁶ Accumulation of unwanted waste substances inside lysosomes can initiate a cascade of secondary effects, ultimately leading to irreversible cellular damage, cell death as well as organ dysfunction and degeneration.⁷

44. Mutations in the GLA gene cause a rare LSD called Fabry disease. The GLA gene encodes the α -Gal A enzyme and mutations in the GLA gene result in either total or partial deficiency of α -Gal A enzyme activity.⁸ α -Gal A is responsible for breaking down various substances, or substrates. For example, α -Gal A breaks down globotriaosylceramide, “GL-3” or “Gb3” and its derivatives, like globotriasosylsphingosine “lysoGb3.”⁹ α -Gal A deficiencies cause accumulation of GL-3 and lysoGb3 in cells throughout the body, including capillary endothelial cells, renal cells, cardiac cells, and nerve cells.¹⁰ Over time, increases in substances

⁵ See Sun, A., (2018) Lysosomal Storage Disease Overview, *Ann. Transl. Med.* **6**(24):476 (ATGAL_10161327 at -327); Gros, F., Muller, S., (2023) The Role of Lysosomes in Metabolic & Autoimmune Diseases, *Nature Revs. Nephrology* **19**:366–83 (ATGAL_10161508 at -509, -513, -521).

⁶ Platt, F.M., (2018) Lysosomal Storage Diseases, *Nat rev Dis Primers* **4**(1):27 (ATGAL_10161649 at -649).

⁷ Platt, F.M., (2018) Lysosomal Storage Diseases, *Nat rev Dis Primers* **4**(1):27 (ATGAL_10161649 at -649); Gros, F., Muller, S., (2023) The Role of Lysosomes in Metabolic & Autoimmune Diseases, *Nature Revs. Nephrology* **19**:366–383 (ATGAL_10161508 at -519–20).

⁸ Ortiz A., (2018) Fabry disease Revisited: Management and Treatment Recommendations for Adult Patients, *Molecular Genetics and Metabolism* **123**(4): 416–427 (ATGAL_09818528 at -528).

⁹ Germain, D., (2010) Fabry Disease, *Orphanet J. of Rare Dis.* **5**:30 (ATGAL_10034456 at -456, -479).

¹⁰ Germain, D., (2010) Fabry Disease, *Orphanet J. of Rare Dis.* **5**:30 (ATGAL_10034456 at -456–57).

such as GL-3 and IsoyGb3 cause cellular damage, narrowing of the vasculature, reduced circulation, and inadequate tissue nourishment.¹¹

45. Fabry disease is an X-linked disorder because the GLA gene is located on the X chromosome.¹² Males, having only one X chromosome, possess a single copy of the GLA gene. A mutation in the GLA gene in a male patient leads to reduced or absent α -Gal A activity in all of the cells in the body.¹³ Females have two copies of the GLA gene because females have two X chromosomes. However, one copy of the GLA gene is active as one chromosome is silenced through X-inactivation.¹⁴ For a female patient with Fabry disease, she has one copy of the GLA gene that is mutated and one copy that is wild type, that expresses normal α -Gal A. Depending on which X chromosome is inactivated in a cell, the remaining X chromosome can have either a normal GLA gene or a mutated GLA gene.¹⁵ For such a female Fabry patient, roughly half of the cells will diminished or absent α -Gal A activity, while the remaining cells retain normal α -Gal A activity.

46. For both males and females, Fabry disease is a chronic, multisystem disorder that may shorten average life expectancy of Fabry patients to 58 and 75 years for males and females,

¹¹ Desnick, R., Ioannou, Y., Eng, C., α -Galactosidase A Deficiency: Fabry Disease, *Online Metabolic & Molecular Bases of Inherited Disease* (McGraw-Hill Education; 2019), pp. 3733–44 (ATGAL_07011379 at -403).

¹² E.g., Izhar, R. et al., (2023) Fabry Disease in Women: Genetic Basis, Available Biomarkers, & Clinical Manifestations, *Genes* 15(1):37 (ATGAL_10161341 at -341–42).

¹³ Izhar, R. et al., (2023) Fabry Disease in Women: Genetic Basis, Available Biomarkers, & Clinical Manifestations, *Genes* 15(1):37 (ATGAL_10161341 at -342, -353).

¹⁴ Izhar, R. et al., (2023) Fabry Disease in Women: Genetic Basis, Available Biomarkers, & Clinical Manifestations, *Genes* 15(1):37 (ATGAL_10161341 at -342).

¹⁵ Izhar, R. et al., (2023) Fabry Disease in Women: Genetic Basis, Available Biomarkers, & Clinical Manifestations, *Genes* 15(1):37 (ATGAL_10161341 at -342, -353).

respectively.¹⁶ This is considerably shorter than the lifespan of males and females without Fabry disease. For males without Fabry disease, the average life expectancy is 73.2 years and females without Fabry disease, the average life expectancy is 79.1 years.¹⁷

47. The classical, severe form of Fabry disease is caused by changes in the GLA gene that result in no α -Gal A activity.¹⁸ For male patients with classical Fabry disease, it is thought that accumulation of GL-3 starts in utero and the initial stages of organ injury may start at a very early age.¹⁹ The first symptoms, including chronic neuropathic pain and episodic severe pain crises, gastrointestinal symptoms (e.g., abdominal pain, diarrhea), impaired sweating, hearing loss, and fatigue, typically emerge during childhood.²⁰ These patients are characterized by absent or severely reduced ($< 1\%$ of mean normal) α -Gal A activity, significant GL-3 accumulation in vascular endothelial cells, cardiomyocytes, smooth muscle cells, and podocytes.²¹ As the symptoms progress, patients develop increased risk of progressive chronic

¹⁶ Lidove, O. *et al.*, (2016) Fabry in the Older Patient: Clinical Consequences & Possibilities for Treatment, *Mol. Genet. and Metab.* **118**(4):319 (ATGAL_00216964 at -964).

¹⁷ Arias, E. *et al.*, (2022) Provisional Life Expectancy Estimates for 2021, *Nat'l Ctr. for Health Stat. Reps.* 23 (ATGAL_10161364 at -364).

¹⁸ Lidove, O. *et al.*, (2016) Fabry in the Older Patient: Clinical Consequences & Possibilities for Treatment, *Mol. Genet. Metab.* **118**(4):319 (ATGAL_00216964 at -964); Ortiz A., (2018) Fabry disease Revisited: Management and Treatment Recommendations for Adult Patients, *Mol. Genet. and Metab.* **123**(4): 416–427 (ATGAL_09818528 at -529).

¹⁹ Hopkin R.J., (2023) Clinical Outcomes Among Young Patients with Fabry Disease Who Initiated Agalsidase Beta Treatment Before 30 Years of Age: An Analysis from the Fabry Registry, *Mol. Genet. and Metab.* **138**(2):106967 (ATGAL_03927842 at -843).

²⁰ Ortiz A., (2018) Fabry disease Revisited: Management and Treatment Recommendations for Adult Patients, *Mol. Genet. and Metab.* **123**(4): 416–427 (ATGAL_09818528 at -529).

²¹ Hopkin R.J., (2023) Clinical Outcomes Among Young Patients with Fabry Disease Who Initiated Agalsidase Beta Treatment Before 30 Years of Age: An Analysis from the Fabry Registry, *Mol. Genet. and Metab.* **138**(2):106967 (ATGAL_03927842 at -843).

kidney disease, left ventricular hypertrophy (LVH), myocardial fibrosis, arrhythmias, and strokes increases with age, and eventually death.²²

48. Non-classical or late-onset Fabry disease is caused by changes in the gene that result in diminished α -Gal A activity.²³ For patients with non-classical or late-onset Fabry disease, symptoms may be delayed or there may be single-organ involvement.²⁴ Because female patients have varying levels of residual α -GAL A activity ranging from normal to almost no activity depending on the GLA variant and X-chromosome inactivation, phenotype of female patients varies widely in accordance.²⁵ While onset of first symptoms in females generally occurs later than that for classic male patients, it is frequently observed at pediatric ages.²⁶ Adult female patients also have an increased risk for clinical organ involvement and decreased quality of life and overall longevity.²⁷ In patients with the later-onset phenotype, typical cardiac symptoms present in the fourth to seventh decades of life, reflecting delayed onset and slower

²² Ortiz A., (2018) Fabry disease Revisited: Management and Treatment Recommendations for Adult Patients, *Mol. Genet. and Metab.* **123**(4): 416–427 (ATGAL_09818528 at -529).

²³ Lidove, O. *et al.*, (2016) Fabry in the Older Patient: Clinical Consequences & Possibilities for Treatment, *Mol. Genet. and Metab.* **118**(4):319 (ATGAL_00216964 at -964); Ortiz A., (2018) Fabry disease Revisited: Management and Treatment Recommendations for Adult Patients, *Mol. Genet. and Metab.* **123**(4): 416–427 (ATGAL_09818528 at -529).

²⁴ Lidove, O. *et al.*, (2016) Fabry in the Older Patient: Clinical Consequences & Possibilities for Treatment, *Mol. Genet. and Metab.* **118**(4):319 (ATGAL_00216964 at -964).

²⁵ Ortiz A., (2018) Fabry disease Revisited: Management and Treatment Recommendations for Adult Patients, *Mol. Genet. and Metab.* **123**(4): 416–427 (ATGAL_09818528 at -529).

²⁶ Hopkin R.J., (2023) Clinical Outcomes Among Young Patients with Fabry Disease Who Initiated Agalsidase Beta Treatment Before 30 Years of Age: An Analysis from the Fabry Registry, *Mol. Genet. and Metab.* **138**(2):106967 (ATGAL_03927842 at -843).

²⁷ Hopkin R.J., (2023) Clinical Outcomes Among Young Patients with Fabry Disease Who Initiated Agalsidase Beta Treatment Before 30 Years of Age: An Analysis from the Fabry Registry, *Mol. Genet. and Metab.* **138**(2):106967 (ATGAL_03927842 at -843).

disease progression.²⁸ As of 2025, more than 1,000 distinct mutations in the GLA gene that cause Fabry disease have been discovered.²⁹ There is no clear mutational hot spot for GLA mutations and mutations that cause Fabry disease can be found across the entire GLA gene.³⁰ There have been a number of different types of Fabry-associated GLA mutations identified, including missense, nonsense, mutations affecting splicing, and frameshift mutations (small and large deletions and insertions) as causing Fabry disease.³¹ Missense point mutations, which generally result in single amino acid changes in the α -Gal A enzyme, make up about 60% of Fabry associated mutations.³² The specific missense point mutation influences the activity of the mutated α -Gal enzyme, leading to clinical presentations that range from classical to non-classical Fabry disease. In general, nonsense, consensus splice site, and most frameshift mutations result in little or no α -Gal A enzyme activity, and are associated with the classic phenotype. In contrast, a proportion of the missense mutations and rare cryptic splicing mutations can result in enzymes with residual α -Gal A activity, which may explain the later-onset phenotypes.³³ Both classical and non-classical Fabry disease may be treatable with chaperone therapies.

²⁸ Ortiz A., (2018) Fabry disease Revisited: Management and Treatment Recommendations for Adult Patients, *Mol. Genet. and Metab.* **123**(4): 416–427 (ATGAL_09818528 at -529).

²⁹ Anania, M. *et al.*, (2025) Identification of Four New Mutations in the GLA Gene Associated with Anderson–Fabry Disease, *Int. J. Mol. Sci.* 26(2):473 (ATGAL_10161380 at -386).

³⁰ Gal, A., Schafer, E., Rohard, I., The Genetic Basis of Fabry Disease, *Fabry Disease: Perspectives from 5 Years of FOS* (NCBI Bookshelf; 2006) (ATGAL_00216171 at -171).

³¹ See Benjamin, E. *et al.*, (2017) The Validation of Pharmacogenetics for the Identification of Fabry Patients to be Treated with Migalastat, *Genet. Med.* **19**(4):436 (ATGAL_07871417 at -423); Ortiz A., (2018) Fabry disease Revisited: Management and Treatment Recommendations for Adult Patients, *Mol. Genet. and Metab.* **123**(4): 416–427 (ATGAL_09818528 at -529).

³² Benjamin, E. *et al.*, (2017) The Validation of Pharmacogenetics for the Identification of Fabry Patients to be Treated with Migalastat, *Genet. Med.* **19**(4):436 (ATGAL_07871417 at -417).

³³ Ortiz A., (2018) Fabry disease Revisited: Management and Treatment Recommendations for Adult Patients, *Mol. Genet. and Metab.* **123**(4): 416–427 (ATGAL_09818528 at -529).

49. Reliable diagnosis of Fabry disease can be challenging, even if the defective α -Gal A enzyme was already characterized.³⁴ Disease manifestations in patients with the same gene mutation, even males from the same family, may vary, making disease management and treatment difficult.³⁵ Factors that will likely alter the impact of a given gene mutation include the presence of additional deleterious GLA variants or variants of unknown significance, the genetic background of the patient, concomitant diseases, and environmental modifiers.³⁶ For males, a key diagnostic marker is the level of α -Gal A enzyme activity. Due to the X-linked aspect of the disease, Fabry disease can be more challenging to diagnose in females.³⁷ Because females have two copies of the GLA gene, they may exhibit normal activity in some tissues, concealing the enzyme function deficiency that leads to diagnosis challenges.³⁸ Further, for patients with non-classical or late-onset Fabry disease, their symptoms may be related to only a single organ, which can complicate diagnosis, especially for those who are not as familiar with the various forms of Fabry disease.³⁹

³⁴ Desnick, R., Ioannou, Y., Eng, C., α -Galactosidase A Deficiency: Fabry Disease, *Online Metabolic & Molecular Bases of Inherited Disease* (McGraw-Hill Ed. 2001), pp. 3733–44 (ATGAL_07011379 at -405).

³⁵ Ortiz A., (2018) Fabry disease Revisited: Management and Treatment Recommendations for Adult Patients, *Mol. Genet. and Metab.* **123**(4): 416–427 (ATGAL_09818528 at -530).

³⁶ Ortiz A., (2018) Fabry disease Revisited: Management and Treatment Recommendations for Adult Patients, *Mol. Genet. and Metab.* **123**(4): 416–427 (ATGAL_09818528 at -530).

³⁷ Wang, R. *et al.*, (2007) Heterozygous Fabry Women Are Not Just Carriers, But Have a Significant Burden of Disease & Impaired Quality of Life, *Genet. Med.* **9**(1):34–45 (ATGAL_08225720 at -720).

³⁸ Wang, R. *et al.*, (2007) Heterozygous Fabry Women Are Not Just Carriers, But Have a Significant Burden of Disease & Impaired Quality of Life, *Genet. Med.* **9**(1):34–45 (ATGAL_08225720 at -720).

³⁹ Michaud, M. *et al.*, (2020) When & How to Diagnose Fabry Disease in Clinical Practice, *Am. J. Med. Scis.* **360**(6):641–49 (ATGAL_10161404 at -404).

50. Education and ability to recognize symptoms of the various presentations of Fabry disease are crucial, because while there are a number of available treatments currently available, those treatments are most effective when initiated early in the disease to prevent organ damage before it occurs. Fabry disease is progressive and, left untreated, Fabry disease results in many severe symptoms, including kidney failure, heart problems, gastrointestinal pain, neuropathic pain, and cerebrovascular problems.⁴⁰ Symptoms of disease progression are patient specific and non-uniform across Fabry patients. A commonality is that the disease progressively worsens over time and, if left untreated, can cause irreversible organ damage and death. This makes early detection and prompt treatment critical for positive patient outcomes.⁴¹

B. Migalastat

51. Migalastat is a low molecular weight iminosugar that binds to the active site of the α -Gal A enzyme.⁴² Depending on its concentration, migalastat can act either as an inhibitor of α -Gal A enzyme activity⁴³ or can act as a pharmacological chaperone for α -Gal A.⁴⁴ “Chaperone” is a term that describes a broad category of molecules that affect protein folding, structure, and stability. When a chaperone is specific to a single target protein, it is referred to as

⁴⁰ Dutra-Clarke, M. *et al.*, (2021) Variable Clinical Features of Patients with Fabry Disease & Outcome of Enzyme Replacement Therapy, *Mol. Genet. and Metab. Reps.* **26**:100700 (ATGAL_10161393 at -393, -395).

⁴¹ *E.g.*, Patient Stories, FSIG, <https://fabry.org/patientstories/> (ATGAL_10161465 at -467–68).

⁴² McCafferty, E., Scott, L., (2019) Migalastat: A Review in Fabry Disease, *Drugs* **79**(5):543–54 (ATGAL_10161438 at -438).

⁴³ Pieroni, M. *et al.*, (2021) Cardiac Involvement in Fabry Disease, *J. Am. Coll. Cardiology* **77**(7):922–36 (ATGAL_10036328 at -337).

⁴⁴ Pieroni, M. *et al.*, (2021) Cardiac Involvement in Fabry Disease, *J. Am. Coll. Cardiology* **77**(7):922–36 (ATGAL_10036328 at -337).

a “pharmacological chaperone.”⁴⁵ Migalastat is one such pharmacological chaperone. In fact, it is the first FDA-approved chaperone.

52. Migalastat protects α -Gal A from degradation by binding reversibly in the cell’s endoplasmic reticulum (“ER”) and allows the stabilized protein to be transported into the lysosome.⁴⁶ In the lysosome, upon its release from migalastat, α -Gal A breaks down its substrates, such as GL-3 and lysoGb3, that accumulate in the cells of Fabry patients.⁴⁷ Unfortunately, migalastat does not have an effect on all mutated α -Gal A proteins causing Fabry disease.⁴⁸ Further, it is almost impossible to predict, a priori, which patients may respond to migalastat. For example, certain mutations lead to production of α -Gal A protein with no enzymatic activity or even no α -Gal A protein. Other mutations result in production of mutant α -Gal A with reduced enzymatic activity due to its decreased stability. Only some GLA mutations produce α -Gal A enzymes that maintain some activity and can be stabilized by migalastat, allowing their transport into the lysosome.

C. Approval of GALAFOLD

53. Amicus has conducted studies of migalastat formulated as an oral chaperone product called GALAFOLD for treatment of Fabry disease. Not all Fabry patients are candidates for treatment with GALAFOLD. The GALAFOLD label identifies specific α -Gal A mutations

⁴⁵ Liguori, L. *et al.*, (2020) Pharmacological Chaperones: A Therapeutic Approach for Diseases Caused by Destabilizing Missense Mutations, *Int. J. Mol. Sci.* **21**(2):489 (ATGAL_04808173 at -173).

⁴⁶ McCafferty, E., Scott, L., (2019) Migalastat: A Review in Fabry Disease, *Drugs* **79**(5):543–54 (ATGAL_10161438 at -438).

⁴⁷ McCafferty, E., Scott, L., (2019) Migalastat: A Review in Fabry Disease, *Drugs* **79**(5):543–54 (ATGAL_10161438 at -438).

⁴⁸ McCafferty, E., Scott, L., (2019) Migalastat: A Review in Fabry Disease, *Drugs* **79**(5):543–54 (ATGAL_10161438 at -438).

that have been determined to be amenable to treatment with GALAFOLD. Amenability refers to the ability of migalastat to stabilize and properly chaperone the mutant α -Gal A enzyme leading to increased enzyme activity when measured using a particular in vitro assay.

54. Initially, Amicus developed assays to measure the effect of migalastat in cells cultured from patients and later developed an in vitro assay using HEK-293 cells to determine which α -Gal A mutations might be responsive to migalastat.⁴⁹ In 2011, in collaboration with GSK, Amicus initiated two Phase 3 pivotal studies of migalastat in treatment-naïve patients (i.e., 011 Study, or FACETS) and patients who switched to migalastat from ERT (i.e., 012 Study, or ATTRACT),⁵⁰ Specifically, Fabry patients with known α -Gal A mutations that seemed responsive to migalastat based on the R&D HEK Assay were selected for enrollment in the two trials. In December 2012, the first six months of data from the 011 Study were unblinded.⁵¹ Unexpectedly, the data revealed that the study failed to meet its endpoints. The data showed that responsiveness in the R&D HEK assay could not be used to accurately predict the clinical response of the study participants in the 011 Study.

55. Meanwhile, Amicus scientists were working to develop and validate a more reliable HEK assay that is described in the Reassessment Mutations Patents as the Migalastat Amenability Assay.

56. [REDACTED]

[REDACTED]

⁴⁹ See e.g., '319 Patent Publication and Wu.

⁵⁰ McCafferty, E., Scott, L., (2019) Migalastat: A Review in Fabry Disease, *Drugs* 79(5):543–54 (ATGAL_10161438 at -438).

⁵¹ Nov. 6, 2012 FDA Advice/Information Request (ATGAL_01221622 at -622); Dec. 19, 2012 Press Release Amicus Therapeutics and GSK Announce Top Line 6-Month Primary Treatment Period Results from First Phase 3 Fabry Monotherapy Study (ATGAL_01109151 at -151).

[REDACTED]⁵² For example, when tested with the R&D HEK Assay, the mutation A13P had no meaningful increase in enzyme activity with migalastat.⁵³ This mutation however, was found to be amenable when tested with the Migalastat Amenability Assay.⁵⁴ [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]⁵⁶ In addition, A20D, G80D, D175E, K213M, M267T, A309V, V316I, V316G, P323R, A352G, R356P, and V390M were separately reported as non-responsive in the literature but were found to be responsive in the Migalastat Amenability Assay.⁵⁷ After the initial data from the 011 Study, Amicus also determined that there was a correlation between amenability as determined by the Migalastat Amenability Assay and clinical response. Because of this

⁵² Oct. 29, 2013 HEK Assay Slides Desnick Visit (ATGAL_09472479 at -487, -512–13).

⁵³ '319 Patent Publication; June 30, 2009 Fabry Mutagenesis Screening Database (showing no meaningful increase in enzyme activity with migalastat under the R&D HEK Assay for Q57L, first tested on July 2, 2008, P146S, first tested under the on August 29, 2007, and I242F, first tested February 26, 2008) (ATGAL_01433113 at -113); June 11, 2012 Data Sheet-xw (further showing T385A and G395A test data failing to meet drug response criteria under the R&D HEK Assay) (ATGAL_00416643 at -643).

⁵⁴ Oct. 29, 2013 HEK Assay Slides Desnick Visit (ATGAL_09472479 at -513).

⁵⁵ Oct. 29, 2013 HEK Assay Slides Desnick Visit (identifying mutations that switched categories) (ATGAL_09472479 at -512–13); Aug 7, 2015 GLP HEK Assay Slides for Jeff (ATGAL_09479478 at -487).

⁵⁶ Oct. 29, 2013 HEK Assay Slides Desnick Visit (ATGAL_09472479 at -513).

⁵⁷ Lukas, J., et al., *Functional and Clinical Consequences of Novel α -Galactosidase A Mutations in Fabry Disease*, HUMAN MUTATION, Vol. 00, No. 0, 1–9 (2015) (ATGAL_00730664); Lukas, J., et al., *Functional Characterisation of Alpha-Galactosidase A Mutations as a Basis for a New Classification System in Fabry Disease*, PLOS GENETICS, Vol 9, Issue 8 (Aug. 2013) (ATGAL_09916904; ATGAL_01136145).

correlation, Amicus was able to determine which patients with known mutations associated with Fabry disease are amenable to migalastat treatment, including at 150 mg every other day

57. After Amicus completed the 011 and 012 Studies,⁵⁸ Amicus filed a new drug application (“NDA”) on December 14, 2017, requesting the approval of migalastat to treat Fabry patients with amenable α -Gal A mutations who are also at least 16 years old.⁵⁹

58. On August 18, 2018, the Food and Drug Administration (“FDA”) approved GALAFOLD (migalastat) to treat adult Fabry patients who have confirmed diagnosis of Fabry disease and an α -Gal A mutation that was determined to be amenable to migalastat treatment using a specific in vitro amenability assay, which is referred to as the Migalastat Amenability Assay in this report.⁶⁰ The approval was under the accelerated approval pathway. This pathway allows FDA to “approve drugs for serious conditions where there is an unmet medical need and where a drug is shown to have certain effects that are reasonably likely to predict a clinical benefit in patients.”⁶¹ The GALAFOLD prescribing information initially identified 348 amenable mutations that were shown to have increased activity in a specified in vitro assay and were deemed to be amenable to migalastat treatment.

59. Later work by Amicus also identified a number of previously unidentified mutations in α -Gal A that are amenable to treatment with migalastat. This work described in the Engineering Mutation Patent has been invaluable to doctors in getting the appropriate treatment

⁵⁸ McCafferty, E., Scott, L., (2019) Migalastat: A Review in Fabry Disease, *Drugs* **79**(5):543–54 (ATGAL_10161438 at -438).

⁵⁹ Dec. 14, 2017 Amicus Announcement, Amicus Therapeutics Submits New Drug Application to U.S. FDA for Migalastat for Treatment of Fabry Disease (ATGAL_05355923 at -923).

⁶⁰ Aug. 10, 2018 FDA News Release, FDA Approves New Treatment for a Rare Genetic Disorder, Fabry Disease (ATGAL_09880475 at -475).

⁶¹ Aug. 10, 2018 FDA News Release, FDA Approves New Treatment for a Rare Genetic Disorder, Fabry Disease (ATGAL_09880475 at -476).

to Fabry patients as quickly as possible after the initial diagnosis. These newly identified amenable mutations were also identified in patients and include the Y184S, N228H, or T412I mutations.

60. Currently, there are 367 amenable α -Gal A mutations identified in the prescribing information.⁶² A list of those amenable α -Gal A mutations is provided in Table 2 of the prescribing information.

D. Response to Dr. Medin's Tutorial

61. Dr. Medin opines that “mutant forms that are most likely to show increased total cellular α -Gal A activity in Fabry patients treated with migalastat are physically unstable, prone to inefficient or aberrant folding, have deficient lysosomal trafficking, and/or show increased levels in cultured cells upon binding and stabilization by migalastat. Such mutant forms are defined as ‘responsive.’”⁶³ I disagree with Dr. Medin's characterization of which mutations may be considered as responsive. As I discuss in this report, while it is now possible to identify mutant α -Gal A forms that are most likely to show increased activity in Fabry patients treated with migalastat based on the Migalastat Amenability Assay, such mutants were not reasonably identifiable using prior assays used to determine whether migalastat increased α -Gal A levels in cultured cells.

62. Dr. Medin ignores that the cell-based HEK assays reported in the literature (including the R&D HEK reported by, e.g., the prior art references he cites and Lukas et al.) are not reasonably predictive of clinical response in Fabry patients. As I discuss above, Amicus tried using the R&D HEK Assay to identify GLA mutations that may be responsive to migalastat

⁶² June 2024 GALAFOLD Prescribing Information, Table 2 (ATGAL_06388594 at -602–13).

⁶³ Medin Opening Report ¶ 52.

as a patient selection tool in their pivotal clinical assays. As Amicus found out six months into the clinical trial, there was insufficient correlation between the mutations identified as responsive in this assay and the patients who did or did not respond to migalastat demonstrating the unreliability of this HEK assay. Dr. Medin does not discuss the fact that the first assay that was reported as reliable was the Migalastat Amenability Assay that is described in the Asserted Patents. Without this assay, there was no way to identify which α -Gal A mutations may be amenable to migalastat without administering migalastat to Fabry disease patients and determining if a patient responds to migalastat.

VII. THE ASSERTED PATENTS AND CLAIMS

63. The Asserted Claims are directed to methods of treating Fabry patients who have the specific α -Gal A mutations listed in the Asserted Claims by administering migalastat.

A. The Reassessment Patents

64. The Reassessment Patents share a common specification and each references a provisional patent application no. 62/512,458 filed on May 30, 2017. As discussed above, I understand from counsel that the priority date for each of the Reassessment Patent Claims is May 30, 2017. I further understand from counsel and from Dr. Medin's report that there is no dispute that the priority date of the Reassessment Patent Claims is May 30, 2017.

65. The common specification describes that "principles and embodiments of the present invention relate generally to the use of pharmacological chaperones for the treatment of Fabry disease."⁶⁴

66. As described in the common specification of the Reassessment Patents, "[m]any human diseases result from mutations that cause changes in the amino acid sequence of a protein

⁶⁴ '388 Patent at 1:22-24.

which reduce its stability and may prevent it from folding properly.”⁶⁵ In cells, proteins generally fold in a specific organelle known as the endoplasmic reticulum, or ER. The cell has developed “quality control mechanisms that ensure that proteins are folded into their correct three-dimensional shape before they can move from the ER to the appropriate destination in the cell, a process generally referred to as protein trafficking.”⁶⁶ Cells often retain misfolded proteins in the ER, leading to their accumulation. Retention of these misfolded proteins in the ER “interrupts their proper trafficking, and the resulting reduced biological activity can lead to impaired cellular function and ultimately to disease.”⁶⁷ In addition, “the accumulation of misfolded proteins in the ER may lead to various types of stress on cells, which may also contribute to cellular dysfunction and disease.”⁶⁸

67. Retention of misfolded proteins in the ER may lead to LSDs. These disorders “are characterized by deficiencies of lysosomal enzymes due to mutations in the genes encoding the lysosomal enzymes.”⁶⁹ The result of ER-retention of misfolded lysosomal enzymes can cause “the pathologic accumulation of substrates of those enzymes.”⁷⁰ Many of the mutations leading to misfolded proteins are missense mutations, which can lead to the production of a less stable enzyme. “These less stable enzymes are sometimes prematurely degraded by the ER-

⁶⁵ ’388 Patent at 1:29-31.

⁶⁶ ’388 Patent at 1:33-37.

⁶⁷ ’388 Patent at 1:42-44.

⁶⁸ ’388 Patent at 1:44-47.

⁶⁹ ’388 Patent at 1:48-51.

⁷⁰ ’388 Patent at 1:51-52.

associated degradation pathway” resulting in the enzyme deficiency in the lysosome, and the pathologic accumulation of substrate.⁷¹

68. Fabry disease is one such disease where mutations in a single gene lead to a misfolded, less-stable lysozyme enzyme α -Gal A that accumulates in the ER. This causes accumulation of “the substrate globotriaosylceramide (GL-3) to accumulate in various tissues and organs.”⁷²

69. As of the May 30, 2017 priority date, there were at least three proposed approaches to treat Fabry disease: (1) enzyme replacement therapy (“ERT”), which involves intravenous infusion of a purified form of the corresponding wild-type protein; (2) substrate reduction, which involves “the use of small molecule inhibitors to reduce production of the natural substrate of deficient enzyme proteins, thereby ameliorating the pathology”; and (3) pharmacological chaperones or small molecule inhibitors that can bind to the α -Gal A to increase the stability of both mutant enzyme and the corresponding wild type enzyme.⁷³

70. The Reassessment Patent Claims are directed to the use of migalastat, a pharmacological chaperone, to treat Fabry patients with certain mutations in their GLA gene that are amenable to treatment with migalastat. As described in the common specifications:

More than 800 Fabry disease-causing GLA mutations have been identified. Approximately 60% are missense mutations, resulting in single amino acid substitutions in the α -Gal A enzyme. Missense GLA mutations often result in the production of abnormally folded and unstable forms of α -Gal A and the majority are associated with the classic phenotype. Normal cellular quality control mechanisms in the endoplasmic reticulum block the transit of these abnormal proteins to lysosomes and target them for

⁷¹ ’388 Patent at 1:57-58.

⁷² ’388 Patent at 1:66-67.

⁷³ ’388 Patent at 2:5-42.

premature degradation and elimination. Many missense mutant forms are targets for migalastat, an α -Gal A-specific pharmacological chaperone.⁷⁴

71. The common specifications further describe:

Mutant forms of α -galactosidase A considered to be amenable to migalastat are defined as showing a relative increase (+10 μ M migalastat) of ≥ 1.20 -fold and an absolute increase (+10 μ M migalastat) of $\geq 3.0\%$ wild-type when the mutant form of α -galactosidase A is expressed in HEK-293 cells (referred to as the “HEK assay”) according to Good Laboratory Practice (GLP)-validated in vitro assay (GLP HEK or Migalastat Amenability Assay). Such mutations are also referred to herein as “HEK assay amenable” mutations.⁷⁵

72. In addition, the common specifications further describe that:

Migalastat is a low molecular weight iminosugar and is an analogue of the terminal galactose of GL-3. In vitro and in vivo pharmacologic studies have demonstrated that migalastat acts as a pharmacological chaperone, selectively and reversibly binding, with high affinity, to the active site of wild-type α -Gal A and specific mutant forms of α -Gal A, the genotypes of which are referred to as HEK assay amenable mutations. Migalastat binding stabilizes these mutant forms of α -Gal A in the endoplasmic reticulum facilitating their proper trafficking to lysosomes where dissociation of migalastat allows α -Gal A to reduce the level of GL-3 and other substrates. Approximately 30-50% of patients with Fabry disease have HEK assay amenable mutations; the majority of which are associated with the classic phenotype of the disease. A list of HEK assay amenable mutations includes at least those mutations listed in Table 1 [of the Reassessment Patents].⁷⁶

The asserted claims of the '388 Patent are Claims 8 and 36. I understand that a dependent claim incorporates the limitations of the claim(s) from which it depends. Claims 8 and 36 of the '388 Patent (bolded below), along with the claims on which they depend, Claims 1 and 7, are recited below:

1. A method of treating Fabry disease, the method comprising administering migalastat to a patient in need thereof, wherein the patient has an α -galactosidase A protein comprising a HEK assay amenable mutation selected from the group consisting of: A13P, A20D, Q57L, G80D, P146S, D175E, K213R, K213M,

⁷⁴ '388 Patent at 16:8-19.

⁷⁵ '388 Patent at 17:7-16.

⁷⁶ '388 Patent at 18:38-54.

I242F, M267T, A309V, V316I, V316G, P323R, A352G, R356P, T385A, V390M, and G395A.

7. The method of claim 1, wherein the mutation is selected from the group consisting of: G80D, P146S, M267T and R356P.

8. The method of claim 1, wherein the mutation is selected from the group consisting of: A13P, A20D, Q57L, G80D, P146S, D175E, K213M, I242F, M267T, A309V, V316I, V316G, P323R, A352G, R356P, T385A, V390M, and G395A.

36. The method of claim 7, wherein the patient is administered about 150 mg of migalastat hydrochloride every other day.

73. The asserted claims of the '489 Patent are Claims 17 and 23. Claims 17 and 23 of the '489 Patent (bolded below), along with the claims on which they depend, Claims 11 and 22, are recited below:

11. A method of treating Fabry disease, the method comprising administering migalastat to a patient in need thereof, wherein the patient has an α -galactosidase A protein comprising a HEK assay amenable mutation selected from the group consisting of A13T, N34T, M42K, L54F, P60T, E87D, L89F, Y123C, H125L, I133M, K140T, F145S, P146R, Y152H, D165G, p.M187_S188dup, V199G, M208R, I219L, N224T, Q250R, G261C, G271D, M284V, I303F, D322N, G325R, K326N, G334E, E358Q, E358D, G361E, G375E, T412N and M421V.

17. The method of claim 11, wherein the patient is administered about 150 mg of migalastat hydrochloride every other day.

22. The method of claim 11, wherein the mutation is selected from the group consisting of: L54F, L89F, K140T and G334E.

23. The method of claim 22, wherein the patient is administered about 150 mg of migalastat hydrochloride every other day.

74. The asserted claim of the '490 Patent is Claim 9. Claim 9 of the '490 Patent (bolded below), along with the claims on which it depends, Claims 1 and 7, are recited below:

1. A method of treating Fabry disease, the method comprising administering migalastat to a patient in need thereof, wherein the patient has an α -galactosidase A protein comprising a HEK assay amenable mutation selected from the group consisting of: I242F, G334E, N34D and p.V254del.

7. The method of claim 1, wherein the patient is administered about 150 mg of migalastat hydrochloride every other day.

9. The method of claim 7, wherein the mutation is I242F.

B. The Engineered Mutations Patent

75. The Engineered Mutations Patent references a provisional patent application no. 62/883,756 filed on August 7, 2019. As discussed above, I understand from counsel that the priority date for each of the Engineered Mutations Patent Claims is August 7, 2019, based on the provisional application. I further understand from counsel and from Dr. Medin's report that there is no dispute that the priority date of the Engineered Mutations Patent Claims is August 7, 2019.

76. The Engineered Mutations Patent Claims are directed to a method of treating a Fabry patient with a previously uncharacterized GLA mutation using migalastat. The specification provides that, "even when Fabry disease is diagnosed by detecting deficient α -Gal A activity in plasma or peripheral leukocytes (WBCs), it is very difficult, if not impossible, to predict whether a particular Fabry patient will respond to treatment with a [pharmacological chaperone]." ⁷⁷ Thus, there remains a need to identify new GLA mutations that will respond to treatment with a pharmacological chaperone and make available new methods of treatment to Fabry patients with such new mutations.

77. While more than 1,000 mutations in the GLA gene have been identified in Fabry patients, the genotype-phenotype correlation is not always clear for every mutation. ⁷⁸ This is partly because of the wide variability in clinical manifestations. For certain mutations in the GLA gene, there is little genotype-phenotype correlation even at the intrafamilial level. ⁷⁹

⁷⁷ '164 Patent at 2:33-37.

⁷⁸ '164 Patent at 24:50-51.

⁷⁹ '164 Patent at 24:62-64.

78. Identification of new mutations increases the molecular knowledge of the GLA gene and provides doctors with support for a correct diagnosis of Fabry disease. Further, identification of engineered mutations that may cause Fabry disease allows doctors to identify pre-symptomatic patients who can start therapy as early as possible before any potential organ damage can become irreversible. In addition, identification of engineered amenable mutations in GLA gene reduces the time between the onset of symptoms and the diagnosis of Fabry disease, avoiding treatment that is not useful for patients and starting the available therapy specific to the mutation each patient has.

79. The claimed treatment method of the Engineered Mutations Patent comprises administering to a patient a therapeutically effective amount of migalastat wherein the patient has a missense mutation in the GLA gene. The specification describes Amicus's efforts to identify previously undetected mutations that are amenable to treatment with migalastat after making and testing in the order of around 2,000 mutations individually in the GLA gene. Tables 2 and 3 include new amenable mutations with specific nucleotide and corresponding amino acid changes. Table 4 includes previously unidentified specific mutations in GLA that were subsequently found in Fabry patients.

80. The asserted claims of the '164 Patent are Claims 23-27. Claims 23-27 of the '164 Patent are recited below:

23. A method for treatment of Fabry disease in a human patient in need thereof, the method comprising orally administering to the patient about 123 mg free base equivalent of migalastat or a salt thereof every other day, wherein the patient has an α -galactosidase A mutation selected from the group consisting of: Y184S, N228H, or T412I.

24. The method of claim 23, wherein the patient is administered about 150 mg of migalastat hydrochloride every other day.

25. The method of claim 23, wherein the patient has the mutation Y184S.

26. The method of claim 23, wherein the patient has the mutation N228H.

27. The method of claim 23, wherein the patient has the mutation T412I.

C. Summary of Mutations in the Asserted Claims

81. The specific mutations identified in the methods of treatment of the Asserted Claims are listed as amenable mutations to migalastat treatment in GALAFOLD's current label.⁸⁰ The specific mutations in each of the Asserted Claims are listed by claim below:

- **Claim 8 of the '388 Patent:** A13P, A20D, Q57L, G80D, P146S, D175E, K213M, I242F, M267T, A309V, V316I, V316G, P323R, A352G, R356P, T385A, V390M, and G395A;
- **Claim 36 of the '388 Patent:** G80D, P146S, M267T, and R356P;
- **Claim 17 of the '489 Patent:** A13T, N34T, M42K, L54F, P60T, E87D, L89F, Y123C, H125L, I133M, K140T, F145S, P146R, Y152H, D165G, p.M187_S188dup, V199G, M208R, I219L, N224T, Q250R, G261C, G271D, M284V, I303F, D322N, G325R, K326N, G334E, E358D, E358Q, G361E, G375E, T412N, and M421V;
- **Claim 23 of the '489 Patent:** L54F, L89F, K140T, and G334E;
- **Claim 9 of the '490 Patent:** I242F;
- **Claims 23–24 of the '164 Patent:** Y184S, N228H, and T412I;
- **Claim 25 of the '164 Patent:** Y184S;
- **Claim 26 of the '164 Patent:** N228H; and
- **Claim 27 of the '164 Patent:** T412I.

VIII. THE ASSERTED CLAIMS ARE NOT OBVIOUS

82. For the reasons discussed in this report, it is my opinion that the Asserted Claims, which are the Reassessment Patent Claims (Claims 8 and 36 of the '388 Patent, Claims 17 and 23 of the '489 Patent, and Claim 9 of the '490 Patent), and the Engineered Mutations Patent

⁸⁰ June 2024 GALAFOLD Prescribing Information, Table 2 (ATGAL_06388594 at -602–13).

Claims (Claims 23-27 of the '164 Patent), are not obvious over any of the asserted prior art combinations that Dr. Medin presents in his opening report.

83. I disagree with Dr. Medin's opinion that "[t]he asserted claims of the '388, '489, '490, and '164 patents claim elements that were well-known in the art before May 30, 2017."⁸¹ As discussed below, the prior art discouraged the use of migalastat to treat the specific Fabry patients claimed in claims 8 and 36 of the '388 Patent and Claim 9 of the '490 Patent. Further, none of the prior art references Dr. Medin relies upon teaches the use of migalastat to treat the specific Fabry patients claimed in Claims 17 and 23 of the '489 Patent. In addition, far from being well-known in the art, the mutations at issue in Claims 23-27 of the '164 Patent had not even been discovered in patients as of August 7, 2019.

84. Similarly, I disagree with Dr. Medin's opinion that "[a] [person of ordinary skill in the art] would have known about the HEK assay long before the earliest claimed priority date and through routine experimentation could determine HEK assay amenable mutations."⁸² In my opinion, the prior art did not teach or suggest which mutations would be amenable to treatment with migalastat. In fact, there were a number of HEK assays in the prior art that could not reliably identify patients who could be treated with migalastat, including Amicus's own R&D HEK Assay and other HEK assays, such as the HEK assay described by Lukas.⁸³

⁸¹ Medin Opening Report, ¶ 124.

⁸² Medin Opening Report, ¶ 125.

⁸³ Jan Lukas et al., *Functional and Clinical Consequences of Novel α -Galactosidase A Mutations in Fabry Disease*, Human Mutation, Vol. 00, No. 0, 1–9 (2015) (ATGAL_00730664 at -665–666); Jan Lukas et al., *Functional Characterisation of Alpha-Galactosidase A Mutations as a Basis for a New Classification System in Fabry Disease*, PLOS Genetics, Vol 9, Issue 8 (Aug. 2013) (ATGAL_09916904 at -910; ATGAL_01136145).

85. Rather, the methods of treatment claimed are the result of over a decade of extensive research and development efforts. There was nothing straightforward about arriving at these methods of treatment in contrast to Dr. Medin's opinion that "[t]he asserted claims are straightforward."⁸⁴

86. It is also my opinion that whether or not a patient has a specific mutation is a distinct question from what methods can be used to treat that patient. In my opinion, Dr. Medin's opinion that "a [person of ordinary skill in the art] would have known long before the earliest claimed priority date how to determine whether a patient had an α -Gal A mutation using routine experimentation" does not mean that a skilled artisan would have known how to treat such a patient or whether migalastat is the optimal treatment for such a patient compared to enzyme replacement therapy.⁸⁵ Moreover, none of the prior art references, which Dr. Medin relies upon, on their own or in various combinations, discloses treatment of any Fabry patients claimed in the asserted claims with migalastat.

87. In addition, it is my opinion that simply because it was known that 150 mg every other day of migalastat hydrochloride could be used to treat a Fabry patient with one mutation does not mean that it was straightforward to determine what dose to use for a Fabry patient with a different mutation.

A. The Asserted Prior Art

88. In his opening report, Dr. Medin relies on six asserted prior art references, which are:

⁸⁴ Medin Opening Report, ¶ 124.

⁸⁵ Medin Opening Report, ¶ 125.

- United States Patent Publication Number (“U.S. Pat. Pub. No.”) 2011/0152319 to Benjamin et al (“the ’319 Patent Publication”) (DEFMIG_0000140);
- U.S. Pat. Pub. No. 2015/0352093 to Lockhart et al. (“Lockhart ’093”) (DEFMIG_0000733);
- Roberto Giugliani et al., *A Phase 2 Study of Migalastat Hydrochloride in Females with Fabry Disease: Selection of Population, Safety and Pharmacodynamic Effects*, 109 Molecular Genetics & Metabolism 86 (2013) (“Giugliani”) (DEFMIG_0000693);
- Dominique Germain et al., *Safety and Pharmacodynamic Effects of a Pharmacological Chaperone on α -Galactosidase A Activity and Globotriaosylceramide Clearance in Fabry Disease: Report from Two Phase 2 Clinical Studies*, 7 Orphanet J. Rare Diseases 1 (2012) (“Germain 2012”) (DEFMIG_0000640);
- Elfrida R. Benjamin et al., *The Validation of Pharmacogenetics in the Identification of Target Fabry Patients for Treatment of Migalastat*, Posters at World Symposium (Mar. 1, 2016) (“Benjamin 2016”) (DEFMIG_0000583); and
- Xiaoyang Wu et al., *A Pharmacogenetic Approach to Identify Mutant Forms of α -Galactosidase A that Respond to a Pharmacological Chaperone for Fabry Disease*, 32 Hum. Mutation 965 (2011) (“Wu”) (DEFMIG_0001119).

89. I have reviewed each of these six asserted prior art references. In my opinion, none of these references teaches or discloses, including in combination, a method of treating Fabry disease patients who have the α -Gal A protein mutations disclosed in the Asserted Claims by administering migalastat to such patients. In addition, in my opinion, none of these references teaches or discloses, including in combination, treating such Fabry disease patients with 150 mg of migalastat hydrochloride every other day.

90. I note that five of Dr. Medin’s prior art references are listed as “References Cited” in the Asserted Patents: the ’319 Patent Publication, Lockhart ’093 (based on its PCT (WO2008134628) and related US 9,056,101), Giugliani, Germain 2012, and Benjamin 2016. Counsel have explained to me that this indicates that those five references were before the

examiner at the United States Patent Office while the examiner was reviewing each of the Asserted Patents to determine whether the Asserted Claims are patentable. I therefore understand that the Patent Office has already considered five of the six prior art references that Dr. Medin relies on in his obviousness analysis and the Patent Office determined that the Asserted Claims were patentable and not obvious over the disclosures in these references.

91. The '319 Patent Publication, Wu, Giugliani, Germain 2012, Lockhart '093, and Benjamin 2016 each describes Amicus's own work, including work from the inventors of the Asserted Patents. Dr. Medin's reliance on only Amicus's own work in his obviousness combinations supports my opinion that the field was not crowded and that there was not significant knowledge in the field at the time of the inventions of the Asserted Claims regarding treatment of Fabry disease with an oral pharmacological chaperone. This is especially true for Fabry disease patients with the mutations that appear in the Asserted Claims. In addition, the fact that Amicus's product, GALAFOLD, is the first and only pharmaceutical chaperone on the market for treatment of Fabry disease today, despite the fact that nearly fifteen years have passed since some of the references on which Dr. Medin relies were published, further supports the nonobviousness of the inventions in the Asserted Claims.

92. In his opening report, Dr. Medin has provided summaries of each of the asserted prior art references he uses for his obviousness combinations.⁸⁶ I disagree with certain statements in the summaries that Dr. Medin provides of the six asserted prior art references. I have included my own summaries as well as responses to Dr. Medin's summaries by reference below.

1. The '319 Patent Publication

⁸⁶ Medin Opening Report, §VIII.A.

93. I respond to Dr. Medin’s summary of the ’319 Patent Publication reference (Medin Opening Report, ¶¶ 91-93) with my own summary.

94. The ’319 Patent Publication is a publication of a U.S. Patent Application, which is assigned to Amicus Therapeutics, Inc. and lists Elfrida Benjamin, Hung V. Do, Xiaoyang Wu, John Flanagan, and Brandon Wustman as inventors. Elfrida Benjamin is also an inventor on each of the Asserted Patents. Xiaoyang Wu is an inventor of the Engineered Mutations Patent. The ’319 Patent Publication was published by the Patent Office on June 23, 2011, and is based on a PCT application, which was filed on February 12, 2009.

95. The ’319 Patent Publication states that a “relatively recent approach to treating some enzyme deficiencies involves the use of small molecule inhibitors to reduce production of the natural substrate of deficient enzyme proteins, thereby ameliorating the pathology.”⁸⁷ The ’319 Patent Publication goes on to say that, previously, “it was discovered that administration of small molecule derivatives of glucose and galactose, which are specific, selective competitive inhibitors for several target lysosomal enzymes, effectively increased the stability of the enzymes in cells in vitro and, thus, increased trafficking of the enzymes to the lysosome.”⁸⁸

96. The ’319 Patent Publication describes that the theory behind this approach is that “since the mutant enzyme protein is unstable in the ER . . . , the enzyme protein is retarded in the normal transport pathway . . . and prematurely degraded” and that “a compound which binds to

⁸⁷ ’319 Patent Publication, ¶ 0012.

⁸⁸ ’319 Patent Publication, ¶ 0013.

and increases the stability of a mutant enzyme, may serve as a ‘chaperone’ for the enzyme and increase the amount that can exit the ER and move to the lysosomes.”⁸⁹

97. It also explains that “successful candidates for [specific pharmacological chaperone (“SPC”)] therapy should have a mutation which results in the production of an enzyme that has the potential to be stabilized and folded into a conformation that permits trafficking out of the ER.”⁹⁰ But the ’319 Patent Publication goes on to explain that:

[w]hile missense mutations outside the catalytic site are more likely to be rescuable using SPCs, there is no guarantee, necessitating screening for responsive mutations. This means that, even when Fabry disease is diagnosed by detecting deficient α -Gal A activity in WBCs, it is very difficult, if not impossible, to predict whether a particular Fabry patient will respond to treatment with an SPC without benefit of the present invention.⁹¹

Because of this unpredictability, the ’319 Patent Publication acknowledges that:

[i]n order to apply SPC therapy effectively, a broadly applicable, fast and efficient method for screening patients for responsiveness to SPC therapy needs to be adopted prior to initiation of treatment. Treatment can then be implemented based on the results of the screening. Thus, there remains in the art a need for relatively non-invasive methods to rapidly assess enzyme enhancement with potential therapies prior to making treatment decisions, for both cost and emotional benefits to the patient.⁹²

98. The ’319 Patent Publication states that the present invention “provides an in vitro method for determining enzyme (e.g., α -galactosidase A, α -glucosidase or glucocerebrosidase) responsiveness to a pharmacological chaperone (e.g., 1-deoxygalactonojirimycin, 1-deoxynojirimycin or isofagomine) in a cell line expressing a mutant form of the enzyme” and

⁸⁹ ’319 Patent Publication, ¶ 0013.

⁹⁰ ’319 Patent Publication, ¶ 0014.

⁹¹ ’319 Patent Publication, ¶ 0014.

⁹² ’319 Patent Publication, ¶ 0015.

that it “provides methods to determine whether a patient with a lysosomal storage disorder will benefit from treatment with a specific pharmacological chaperone.”⁹³

99. The '319 Patent Publication includes Example 1, which states it “provides the in vitro diagnostic assay to determine a Fabry patient's responsiveness to a specific pharmacological chaperone.”⁹⁴ The '319 Patent Publication states that “[o]ver 600 Fabry mutations have been reported, and about 60% are missense.”⁹⁵ It also discloses that “DGJ [1-deoxygalactonojirimycin] is currently being studied in Phase 2 clinical trials as a pharmacological chaperone for the treatment of Fabry disease” and that “the hydrochloride salt of DGJ is known as migalastat hydrochloride (Migalastat).”⁹⁶ It also discloses that “it has been shown that DGJ mediates selective and dose-dependent increases in α -Gal A levels in many Fabry patient-derived lymphoid cell lines.”⁹⁷

100. The '319 Patent Publication also explains that:

To identify additional DGJ-responsive mutations, GripTite 293 MSR, (Invitrogen Corp., Carlsbad, Calif., U.S.A.) cells were transiently transfected with expression vectors containing all known α -Gal A missense mutations and several in-frame small deletions and insertions generated by site-directed mutagenesis. Mutant α -Gal A constructs were transiently expressed in HEK-293 cells. Cells were incubated with increasing concentrations of DGJ and α -Gal A activity was measured in cell lysates. Assay validation has been carried out on more than 35 missense mutations and the results obtained in HEK-293 cells were similar to those obtained from both Fabry patient-derived lymphoid cells and primary T-cell cultures (see U.S. Ser. No. 11/749,512), as well as to the α -Gal A enzyme responses observed in the white blood cells of Fabry patients after oral administration of DGJ in Phase 2 clinical trials.⁹⁸

⁹³ '319 Patent Publication, ¶ 0002.

⁹⁴ '319 Patent Publication, ¶ 0138.

⁹⁵ '319 Patent Publication, ¶ 0139.

⁹⁶ '319 Patent Publication, ¶¶ 0139, 0085.

⁹⁷ '319 Patent Publication, ¶ 0139.

⁹⁸ '319 Patent Publication, ¶ 0139.

The '319 Patent Publication reports the results of the testing with the HEK assay described in several figures and tables. For example, it explains that

[w]ith regard to FIG. 1, mutations identified in italicized text were not tested, while those identified in plain text were α -Gal A mutants that were responsive to DGJ treatment in the transient transfection assay, and those identified in bold and underscored text were not responsive to DGJ treatment in the transient transfection assay.⁹⁹

101. The '319 Patent Publication does not disclose a general method of treating Fabry patients or a method treating Fabry patients irrespective of their mutation, let alone with any specific mutation in the Asserted Claims. The '319 Patent Publication describes treating Fabry patients with specific mutations, none of which are the mutations that appear in the Asserted Claims. The '319 Patent Publication does not disclose a method of treating Fabry patients with any of the specific mutations in the Asserted Claims or a method of treating Fabry patients with any of the specific mutations in the Asserted Claims with 150 mg of migalastat every other day.

102. The '319 Patent Publication includes disclosures related to the A13P, Q57L, P146S, and I242F mutations, which appear in certain of the Asserted Claims. However, the '319 Patent Publication discourages a person of skill in the art from treating Fabry patients with these mutations with migalastat because the '319 Patent Publication discloses that based on the results of the in vitro HEK-293 cell-based assay described in the '319 Patent Publication, none of these four mutations is responsive to treatment with migalastat. In fact, the '319 Patent Publication discloses that each of A13P, Q57L, P146S, and I242F mutations is “[n]on-responsive GLA mutations.”¹⁰⁰

⁹⁹ '319 Patent Publication, ¶ 0142.

¹⁰⁰ '319 Patent Publication, at Fig. 18, Fig. 1A, ¶¶ 0026, 0043, 0177.

103. The '319 Patent Publication discloses that there is no way to predict whether any given Fabry patient with a specific mutation will be responsive or non-responsive to treatment with migalastat prior to testing.¹⁰¹

104. The '319 Patent Publication also discloses that different mutations at positions 16, 34, 112, 224 and 352 will result in different responses to migalastat.¹⁰² In my opinion, a person of ordinary skill in the art would not be motivated to treat Fabry patients with any missense mutations that appear at the same amino acid positions as those described as responsive in the '319 Patent Publication based on the teachings of the '319 Patent Publication and would not expect a reasonable expectation of success in doing so. Further, the '319 Patent Publication does not have any disclosures related to the Migalastat Amenability Assay.

2. Wu

105. I respond to Dr. Medin's summary of the Wu reference (Medin Opening Report, ¶¶ 101-104) with my own summary.

106. Wu is an article describing Amicus's work, which was published in the journal Human Mutation in 2011.

107. Wu discloses that Amicus developed "a cell-based assay in cultured HEK-293 cells to identify mutant forms of α -Gal A that are responsive to [migalastat hydrochloride]."¹⁰³

¹⁰¹ *E.g.*, '319 Patent Publication, ¶ 0150 ("DGJ-responsive and non-responsive mutant forms did not appear to be located to particular regions or domains on the α -Gal A protein structure."); '319 Patent Publication, ¶ 0146 ("No significant correlation between response and location on the protein sequence of a mutation was observed, suggesting that responsive as well as non-responsive mutations are distributed widely across the entire protein.").

¹⁰² '319 Patent Publication, at Fig. 17 (showing responsive mutations L16H, N34K, R112H, N224S, A352V); '319 Patent Publication, Fig. 18 (showing non-responsive mutations L16P, N34S, R112C, R112S, N224D, A352P, A352D).

¹⁰³ Wu at 965.

Wu reports results from this HEK-293 cell-based assay for specific mutations, none of which are the mutations in the Asserted Claims.¹⁰⁴ Wu discloses that “evaluation of the utility of the HEK-293 cell-based assay for Fabry patient selection for treatment with [migalastat hydrochloride] is ongoing.”¹⁰⁵ Wu also discloses specific Phase 2 clinical trial data from FAB-CL-201, FAB-CL-202, and FAB-CL-203.¹⁰⁶

108. Wu does not disclose a method of treating Fabry patients with any of the specific mutations in the Asserted Claims or a method of treating Fabry patients with any of the specific mutations in the Asserted Claims with 150 mg of migalastat every other day. Further, Wu does not have any disclosures related to the Migalastat Amenability Assay.

3. Germain 2012

109. I respond to Dr. Medin’s summary of the Germain 2012 reference (Medin Opening Report, ¶¶ 105-111) with my own summary.

110. Germain 2012 is an article published in the Orphanet Journal of Rare Diseases in 2012. Germain 2012 describes two phase 2 studies conducted by Amicus. The phase 2 studies are of nine males with Fabry disease, with eight unique α -Gal A mutations (L415P, P259R, R301Q, F295C, C94S, R112C, N215S, P205T).¹⁰⁷ Germain 2012 discloses that a “HEK-293 assay was retrospectively used to define if a patient carrying a GLA mutation was amenable to

¹⁰⁴ Wu at Table 1.

¹⁰⁵ Wu at 976.

¹⁰⁶ Wu at Table 2.

¹⁰⁷ Germain 2012 at Table 1, Abstract.

migalastat HCl.”¹⁰⁸ Of the eight unique mutations in the phase 2 studies here, five are reported to be amenable and three are reported to be non-amenable using the assay described.¹⁰⁹

111. Germain 2012 discloses that “[a]s these studies included only 9 patients carrying 8 different missense mutations, results should be interpreted with caution” and “[t]he predictive value of the assay will have to be confirmed in larger numbers of [Fabry disease] patients with additional mutations.”¹¹⁰ Germain 2012 also discloses that “[t]his assay is currently used to select patients for phase 3 clinical studies.”¹¹¹ However, a skilled artisan would have understood that the initial data from those phase 3 clinical studies was reported by Amicus as “not meet[ing] statistical significance.”¹¹²

112. Germain 2012 discloses that “[t]his study describes the first use in patients of an oral small molecule pharmacological chaperone, rather than using enzyme replacement therapy, to treat a lysosomal storage disorder.”¹¹³ Germain 2012 also discloses that this study “shows for the first time in medicine that such drug increases the activity, or effectively rescues the mutated and dysfunctional enzyme that patients with Fabry disease have expressed their entire lives.”¹¹⁴ A skilled artisan in this field would have understood this disclosure to mean that the state of the

¹⁰⁸ Germain 2012 at 4.

¹⁰⁹ Germain 2012 at Table 1.

¹¹⁰ Germain 2012 at 9.

¹¹¹ Germain 2012 at 9.

¹¹² Amicus Website, Press Release dated Feb. 15, 2013, available at <https://ir.amicusrx.com/news-releases/news-release-details/amicus-therapeutics-presents-additional-6-month-results-phase-3>.

¹¹³ Germain 2012 at 10.

¹¹⁴ Germain 2012 at 10.

field was in its infancy and that there were not well-understood methods of treatment using pharmacological chaperones generally and specifically using migalastat.

113. Germain 2012 does not disclose a method of treating Fabry patients with any of the specific mutations in the Asserted Claims or a method of treating Fabry patients with any of the specific mutations in the Asserted Claims with 150 mg of migalastat every other day. In addition, Germain 2012 teaches away from the inventions in the Asserted Claims because Germain 2012 notes that “[t]he *in vitro* HEK-293 cell-based assay appears to predict the clinical pharmacodynamic response.”¹¹⁵ However, the inventors of the Reassessment Patents found that the results from the HEK assay described in Germain 2012 (and similar assays performed by others) did not always give accurate results and therefore would not reliably predict the clinical response to migalastat. Further, Germain 2012 does not have any disclosures related to the Migalastat Amenability Assay.

4. Giugliani

114. I respond to Dr. Medin’s summary of the Giugliani reference (Medin Opening Report, ¶¶ 116-118) with my own summary.

115. Giugliani is an article published in the Molecular Genetics and Metabolism journal in 2013. It describes one of Amicus’s phase 2 studies that included nine females with Fabry disease who were administered doses of migalastat hydrochloride at 50 mg, 150 mg, or 250 mg every other day for a period of 12 weeks with extension to 48 weeks.¹¹⁶ These nine female Fabry patients had eight unique α -Gal A mutations (P259R, P205T, R112H, L32P, C52G,

¹¹⁵ Germain 2012 at 9.

¹¹⁶ Giugliani at Abstract.

R227X, E358K, and M1L).¹¹⁷ Giugliani discusses a HEK-293 assay that “was retrospectively used to categorize each study patient’s GLA mutation as either ‘amenable’ or ‘non-amenable’ to chaperone treatment.”¹¹⁸ Of the nine female Fabry patients, five had amenable mutations and four had non-amenable mutations.¹¹⁹

116. Giugliani discloses that “[a]lthough the study results were more favorable in patients with amenable mutations, further clinical investigation of migalastat HCl in all [Fabry disease] females, including those with non-amenable mutations, may be warranted.”¹²⁰

Giugliani also discloses that:

As migalastat HCl selectively and reversibly binds to both mutant and wild type α -Gal A, it is not possible to differentiate which chaperoning is responsible for the activity seen in female patients with [Fabry disease]. In theory, therapeutic benefit in females might result from migalastat HCl-mediated elevation and secretion of wild-type α -Gal A from healthy cells and subsequent cross-correction following uptake into neighboring mutant cells. Thus, heterozygous Fabry patients may potentially be candidates for migalastat HCl treatment, since they express wild-type α -Gal A, which is responsive. However, this mechanism is highly speculative and would have to be supported by further studies.¹²¹

Giugliani further discloses that “[t]his study had several limitations.”¹²² Giugliani explains that:

Due to its small size, descriptive statistics were used to derive qualitative conclusions regarding response to treatment with migalastat HCl. Because the study included 5 patients with amenable mutations and 4 patients with non-amenable mutations with 3 different dose levels, conclusions around dose-response are premature. PTCs are the only kidney cells available for a reliable and quantifiable assessment of decline in GL-3 inclusions, but the GL-3 burden was minimal in kidney PTCs, making assessment of GL-3 decline difficult.¹²³

¹¹⁷ Giugliani at Table 2.

¹¹⁸ Giugliani at 89.

¹¹⁹ Giugliani at Table 2.

¹²⁰ Giugliani at 90.

¹²¹ Giugliani at 90.

¹²² Giugliani at 90.

¹²³ Giugliani at 90.

In my opinion, a skilled artisan would understand these disclosures to mean that the results of the Phase 2 study described in Giuliani cannot be extrapolated to all Fabry patients.

117. Giuliani does not disclose a method of treating Fabry patients with any of the specific mutations in the Asserted Claims or a method of treating Fabry patients with any of the specific mutations in the Asserted Claims with 150 mg of migalastat every other day. Further, Giuliani does not have any disclosures related to the Migalastat Amenability Assay.

5. Lockhart '093

118. I respond to Dr. Medin's summary of the Lockhart '093 reference (Medin Opening Report, ¶¶ 94-100) with my own summary.

119. Lockhart '093 is a publication of a U.S. patent application. The face of the reference lists the publication date as December 10, 2015.

120. Lockhart '093 discusses dosing regimens for administering specific pharmacological chaperones for treatment of lysosomal storage disorders.¹²⁴ Lockhart '093 notes that there are “about fifty known [lysosomal storage disorders] to date, which include Gaucher disease, Fabry disease, Pompe disease, Tay Sachs disease and the mucopolysaccharidoses (MPS).”¹²⁵ Lockhart '093 states that “[t]he present invention provides a dosing regimen and rationale therefore for the use of small molecule competitive inhibitors as pharmacological chaperones for the treatment of lysosomal storage diseases,”¹²⁶ and that “three

¹²⁴ See Lockhart '093, ¶ 0044 (“The present invention provides dosing regimens for administering specific pharmacological chaperones for the treatment of diseases associated with misfolded proteins (e.g., lyso[so]mal storage disorders) and diseases which may be treated or ameliorated with the pharmacological chaperone described herein.”).

¹²⁵ Lockhart '093, ¶ 0006.

¹²⁶ Lockhart '093, ¶ 0002.

pharmacological chaperones are in human clinical trials for Fabry disease, Gaucher disease, and Pompe disease.”¹²⁷

121. Lockhart '093 describes numerous possible dose regimens that could be explored for DGJ.¹²⁸ It does not identify the effective or preferred dose of DGJ for any specific Fabry patients. Lockhart '093 provides an example of a dose regimen for treatment of Fabry disease using DGJ hydrochloride in Example 4, which describes a study design in which patients are given a daily dose of 250 mg/day for 7 days and then 150 mg every other day.¹²⁹ Lockhart '093 does not report data from this study.¹³⁰ Lockhart '093 provides another example of dose regimens for treatment of Fabry disease using DGJ hydrochloride in Example 5, which describes a study of eight patients receiving an ascending dose of 25, 100, and then 250 mg twice a day over six weeks, followed by 50 mg per day for the rest of the study and three patients receiving 150 mg every other day throughout the entire study.¹³¹ Lockhart '093 provides another example of dose regimens for treatment of Fabry disease using DGJ hydrochloride in Example 6, which describes a study of eighteen male and nine female Fabry patients.¹³² Nine male patients received an ascending dose of 25, 100, and 250 mg twice a day for 6 weeks followed by 6 weeks of either 25 mg twice a day or 50 mg per day.¹³³ Four male patients received 150 mg every other day for 12 weeks and five received 150 mg every other day for 24 weeks.¹³⁴ The nine female

¹²⁷ Lockhart '093, ¶ 0010.

¹²⁸ See Lockhart '093, ¶¶ 0184-202.

¹²⁹ Lockhart '093, ¶¶ 0287.

¹³⁰ Lockhart '093, ¶¶ 0283-311.

¹³¹ Lockhart ¶ 0316.

¹³² See Lockhart '093, ¶¶ 0323-368.

¹³³ See Lockhart '093, ¶ 0327.

¹³⁴ See Lockhart '093, ¶ 0327.

patients were randomized to one of three dosages 50, 150, or 250 mg every other day for 12 weeks.¹³⁵ The proposed claims have a similarly expansive set of potential dose regimens. For example, proposed claim 112 has a dose from about 50 mg to about 300 mg of DGJ every two to three days.¹³⁶

122. Lockhart '093 does not disclose a method of treating Fabry patients with any of the specific mutations in the Asserted Claims, nor does it disclose a method of treating Fabry patients with any of the specific mutations in the Asserted Claims with 150 mg of migalastat every other day. The disclosures in Lockhart '093 of any clinical studies are limited to specific Fabry patients with specific mutations, none of which are the mutations in the Asserted Claims. Further, only a small subset of the patients described in Lockhart '093 received 150 mg of migalastat every other day, and none of those patients were Fabry patients with the specific mutations in the Asserted Claims. In addition, Lockhart '093 did not provide any suggestion or motivation to choose 150 mg every other day rather than one of the many other options for dose regimens discussed in the examples. Dr. Medin relies on one paragraph that states:

Since DGJ has a much shorter plasma half-life than [isofagomine (IFG), a chaperone considered as a treatment option for Gaucher disease at the time], the optimal Maintenance Dose is likely to be shorter than for IFG following the Initial Enzyme Build-Up Phase. As one example, it is predicted that administration of 150 mg DGJ every other day for 28 days will result in a plasma concentration above the EC₅₀ for about 16 hours on the day the dose is administered, and below the IC₅₀ for the remaining 8 hours (FIG. 6). On the second day when no drug is administered, the plasma concentration is expected to be below the IC₅₀ until the following day when the drug is administered again (FIG. 6). This pattern continues for the duration of the treatment period.¹³⁷

¹³⁵ See Lockhart '093, ¶ 0327.

¹³⁶ Lockhart '093, cl. 112.

¹³⁷ Lockhart '093, ¶ 0155 (cited and quoted out of context in Medin Opening Report, ¶ 100).

In my opinion, Lockhart '093 is discussing a theory that has not yet been tested or verified rather than “recommend[ing] an ‘optimal’ dose” as Dr. Medin claims. Further, the data in Table 4 that Dr. Medin is citing for support was not even data from Fabry patients; it is data from healthy volunteers.¹³⁸ Thus, in my opinion, Lockhart '093 does not disclose a migalastat dosing regimen for treatment of Fabry patients with the specific mutations included in the Asserted Claims. Further, Lockhart '093 does not have any disclosures related to the Migalastat Amenability Assay.

6. Benjamin 2016

123. I respond to Dr. Medin’s summary of the Benjamin 2016 reference (Medin Opening Report, ¶¶ 112-115) with my own summary.

124. Benjamin 2016 is a poster that reflects work from Amicus scientists. Specifically, Benjamin 2016 discusses a new assay that Amicus was working on and Amicus’s objective of assessing the clinical validation of this new assay.¹³⁹ Benjamin 2016 provides a high-level overview of the assay, but does not provide enough detail for an ordinarily skilled artisan to identify or determine which α -Gal A mutations might be amenable to migalastat treatment.¹⁴⁰ Specifically, Benjamin 2016 includes the following description of the assay:¹⁴¹

¹³⁸ Lockhart '093, ¶ 0154 (cited and quoted out of context in Medin Opening Report, ¶ 100).

¹³⁹ Benjamin 2016 at 3.

¹⁴⁰ Benjamin 2016 at 3-4.

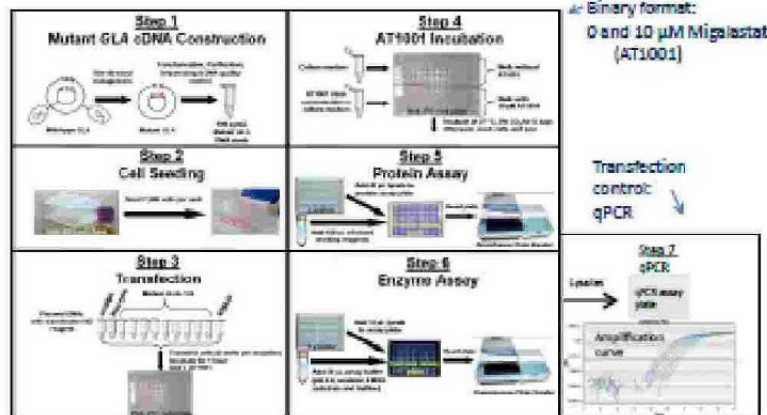
¹⁴¹ Benjamin 2016 at 3-4.

Materials & Methods

Migalastat Amenability Assay (GLP HEK Assay):

- A bioanalytically validated assay used to individually express FD mutations in human embryonic kidney-293 (HEK) cells and measure increases in mutant α -Gal A activity in response to 10 μ M migalastat
- Known FD associated missense, carboxyl-terminal nonsense, small in-frame insertion, deletion, and complex mutant forms of the enzyme qualify for testing in the Migalastat Amenability Assay
- Amenable mutant forms are defined as those having a ≥ 1.2 -fold relative increase and $\geq 3.0\%$ absolute increase in α -Gal A activity
- Patient samples are not required and the approach is applicable to both males and females
- To date, 600 FD mutations have been tested; 268 have met the amenable mutation criteria

Migalastat Amenability Assay Procedure and Data Overview



- The assay includes: A) a thorough and rigorous set of plasmid DNA quality control assessments and storage specifications; B) a simple binary design wherein GLA transfected HEK-293 cells are incubated in the absence or presence of a single concentration of migalastat (10 μ M); C) a quantitative real-time PCR (qPCR) transfection efficiency control measurement obtained from every sample; D) rigorous and consistent assay acceptance criteria

And while Benjamin 2016 discloses that the Migalastat Amenability Assay was able to accurately predict clinical response based on clinical trial data, Benjamin 2016 does not identify or disclose any α -Gal A mutations that are amenable to migalastat treatment.¹⁴²

¹⁴² Benjamin 2016 at 5-7.

125. Dr. Medin ignores that Benjamin 2016 does not disclose a method of treating Fabry patients with any of the specific mutations in the Asserted Claims. Benjamin 2016 also does not disclose a method of treating Fabry patients with any of the specific mutations in the Asserted Claims with 150 mg of migalastat every other day. Thus, the disclosures in Benjamin 2016 would not allow a person of ordinary skill in the art to arrive at the claimed inventions of the Asserted Claims.

126. Without knowing which mutations are amenable in the assay disclosed in Benjamin 2016, a person of ordinary skill in the art would not be motivated to treat any specific Fabry disease patient with migalastat, including with 150 mg of migalastat every other day, based on Benjamin 2016's disclosures.

B. Response to Dr. Medin's Motivation to Combine Arguments

127. Dr. Medin's report includes a general "[m]otivation to [c]ombine or [m]odify" section that is not specific to any of his asserted obviousness combinations.¹⁴³ As a preliminary matter, I have been informed by counsel that the analysis of what would motivate a person of ordinary skill in the art should be based on a specific combination of references. Dr. Medin's report, however, does not provide any arguments regarding why a person of ordinary skill in the art would be motivated to combine or modify the specific references set forth in his obviousness combinations with the other specific references in his obviousness combinations (for example, using Dr. Medin's first alleged combination, why a person of ordinary skill in the art would be motivated to combine or modify the '319 patent publication with "Lockhart '093 and the knowledge of a POSA [person of ordinary skill in the art]"). To the extent that Dr. Medin's

¹⁴³ Compare Medin Opening Report, ¶ 13 (the alleged obviousness combinations) with ¶¶ 119-123 (section on "Motivation to Combine or Modify").

general assertions on motivation can be applied to one of his specific obviousness combinations, I have addressed that in my analysis of each claim below.

128. In addition, I disagree with Dr. Medin's opinions in this section because none of the prior art references he relies upon discloses the elements of the Asserted Claims, including the mutations in the Asserted Claims. In fact, none of the mutations in the Asserted Claims are disclosed as responsive by the cited prior art references. Further, the field was relatively nascent and treatment with migalastat was unpredictable and not advisable for patients with mutations that were determined to be non-responsive to migalastat; and in some cases, the prior art references teach away from the inventions in the Asserted Claims.

C. Claims 8 and 36 of the '388 Patent

129. As an initial matter, it is unclear to me what combination of references Dr. Medin is using for his prior art combinations for Claims 8 and 36 of the '388 Patent. Dr. Medin opines in the summary of his opinions that:

[b]y way of example, the asserted claims are rendered obvious by the following combinations:

- 1) The '319 patent publication in view of Lockhart 093 and the knowledge of a [person of ordinary skill in the art]
- 2) Wu, Germain [2012], Benjamin [2016], and/or Giuliani and the knowledge of a [person of ordinary skill in the art]
- 3) Wu and/or Germain [2012] in view of Benjamin [2016] and/or Giuliani and the knowledge of a [person of ordinary skill in the art.]¹⁴⁴

Dr. Medin seems to imply that there could be additional combinations, but he does not explicitly disclose what those additional combinations might be. Accordingly, I will respond to the opinions and specific combinations that Dr. Medin actually analyzed in his report, and I reserve

¹⁴⁴ Medin Opening Report, ¶ 13.

the right to respond to any additional combinations should Dr. Medin later render an opinion as to such combinations.

130. Moreover, this list results in dozens of possible combinations of the prior art references. Dr. Medin does not actually analyze each of these combinations in his report. Thus, it is unclear what teaching(s) Dr. Medin proposes to take from each reference and why a person of ordinary skill in the art would have been motivated to combine those elements or teachings with a reasonable expectation of success. Instead, Dr. Medin's only obviousness analysis is him analyzing six references, the '319 Patent Publication, Lockhart '093, Wu, Germain 2012, Benjamin 2016, and Giugliani individually without specifying how to combine them within the context of his proposed obviousness combinations let alone why a person of ordinary skill in the art would be motivated to combine those references in such a way. For example, Dr. Medin fails to explain what reference he is starting with and how he is modifying such reference with the other prior art references.¹⁴⁵ Accordingly, I will respond to the opinions that Dr. Medin actually included in his report regarding the disclosed combinations, and I reserve the right to respond to any additional opinions about those combinations should Dr. Medin later render any opinion about what and how the specific references are to be combined and/or the motivation to combine or modify such specific references.

1. Claim 8

131. Claim 8 of the '388 Patent (bolded below) depends from Claim 1. The claim language is:

1. A method of treating Fabry disease, the method comprising administering migalastat to a patient in need thereof, wherein the patient

¹⁴⁵ Medin Opening Report, § IX.B (element by element analysis of the asserted claims of the '388 patent); Medin Opening Report, Exhibit C (claim chart including list of citations to each of the six asserted prior art references without separating by combination).

has an α -galactosidase A protein comprising a HEK assay amenable mutation selected from the group consisting of: A13P, A20D, Q57L, G80D, P146S, D175E, K213R, K213M, I242F, M267T, A309V, V316I, V316G, P323R, A352G, R356P, T385A, V390M, and G395A.

8. The method of claim 1, wherein the mutation is selected from the group consisting of: A13P, A20D, Q57L, G80D, P146S, D175E, K213M, I242F, M267T, A309V, V316I, V316G, P323R, A352G, R356P, T385A, V390M, and G395A.

132. Based on my review of Dr. Medin's report, it is unclear what combinations Dr. Medin asserts for Claim 8. Dr. Medin lists only the following combinations in the summary of his opinions:

- 1) The '319 patent publication in view of Lockhart '093 and the knowledge of a person of ordinary skill in the art;
- 2) Wu, Germain [2012], Benjamin 2016, and/or Giugliani and the knowledge of a person of ordinary skill in the art;
- 3) Wu and/or Germain [2012] in view of Benjamin 2016 and/or Giugliani and the knowledge of a person of ordinary skill in the art.¹⁴⁶

133. Regarding the first combination—the '319 Patent Publication in view of Lockhart '093 and the knowledge of a person of ordinary skill in the art—Dr. Medin does not discuss Lockhart '093 at all for Claim 8.¹⁴⁷ Thus, it is unclear whether Dr. Medin is relying on the first combination for Claim 8. It is possible that Dr. Medin modified that combination for Claim 8 to simply the '319 Patent Publication in view of the knowledge of a person of ordinary skill in the art.¹⁴⁸ But even so, Dr. Medin did not identify what knowledge a person of ordinary skill in the art would have had that is relevant to this combination or why a person of ordinary skill in the art

¹⁴⁶ Medin Opening Report, ¶ 13.

¹⁴⁷ Medin Opening Report, ¶¶ 126-142, Ex. C at '388 Patent Claims 1 & 8.

¹⁴⁸ See Medin Opening Report, ¶ 133 ("Accordingly, claims 1 and 8 would have been obvious over the '319 Patent Publication and the knowledge of a POSA [person of ordinary skill in the art].").

would have been motivated to use that knowledge to modify what is disclosed in the '319 Patent Publication.

134. Regarding the second combination—Wu, Germain 2012, Benjamin 2016, and/or Giugliani, and the knowledge of a person of ordinary skill in the art—it is unclear exactly which of those references he is combining and how those references are being combined. Dr. Medin discusses each of the four references individually before alleging in a conclusory fashion that they could be combined with no explanation of how they would be combined.¹⁴⁹ Dr. Medin again failed to identify what knowledge a person of ordinary skill in the art would have had that is relevant to this combination or why a person of ordinary skill in the art would have been motivated to use that knowledge to modify what is disclosed in the references cited by Dr. Medin.

135. Regarding the third combination—Wu and/or Germain 2012 in view of Benjamin 2016 and/or Giugliani and the knowledge of a person of ordinary skill in the art—it is unclear exactly which of those references he is combining and how those references are being combined. Like with the second combination, Dr. Medin discusses each of the four references individually before alleging in a conclusory fashion that they would be combined, with no explanation of how

¹⁴⁹ See Medin Opening Report, ¶ 142 (“In addition, a POSA [person of ordinary skill in the art] would have been motivated to combine the teachings of Wu, Germain [2012], Giugliani and/or Benjamin (2016) because they all have complementary teachings and show consistent outcomes, therefore, a POSA [person of ordinary skill in the art] would also have an expectation of success in doing so.”); *see also* ¶ 141 (“A POSA [person of ordinary skill in the art] would have been motivated with a reasonable expectation of success to combine the teachings of Wu, Germain 2012, Benjamin (2016), and/or Giugliani, at least because each is directed to the use of migalastat in the treatment of Fabry disease and/or the evaluation of mutations in the α -galactosidase A gene in patients with Fabry disease that inform treatment options for Fabry disease, including treatment with migalastat.”).

they would be combined or why a person of ordinary skill in the art would combine them.¹⁵⁰

Again, Dr. Medin failed to identify what knowledge a person of ordinary skill in the art would have had that is relevant to this combination or why a person of ordinary skill in the art would have been motivated to use that knowledge to modify what is disclosed in the references cited by Dr. Medin.

136. In my opinion, as discussed further below, Dr. Medin’s combinations do not disclose the limitations of Claim 8 and do not render Claim 8 obvious.

a) Asserted Combination 1: the ’319 Patent Publication and the Knowledge of a Person of Ordinary Skill in the Art

137. To support his obviousness opinions, Dr. Medin cites paragraphs 84-85 and Claim 10 of the ’319 Patent Publication to argue that methods for treating Fabry with migalastat was known.¹⁵¹ Dr. Medin also opines that the ’319 Patent Publication “discloses a method of treating Fabry disease by administering migalastat to a patient.”¹⁵² I disagree. The ’319 Patent Publication discloses results of an in vitro HEK assay with respect to specific mutations.

138. Paragraphs 84-85 of the ’319 Patent Publication disclose that 1-deoxygalactonojirimycin (“DGJ” or “migalastat”) and its hydrochloride salt can be pharmacological chaperones.¹⁵³ In my opinion, the disclosure of migalastat and its potential role as a pharmacological chaperone in the ’319 Patent Publication does nothing to disclose or render

¹⁵⁰ See Medin Opening Report, ¶ 141 (“Furthermore, a POSA [person of ordinary skill in the art] seeking to improve upon the existing treatments of Fabry disease would have been motivated with a reasonable expectation of success to combine the disclosures of Wu, and/or Germain 2012 in view of Benjamin (2016) and/or Giugliani, and the knowledge of a POSA [person of ordinary skill in the art].”).

¹⁵¹ Medin Opening Report, ¶ 127, Ex. C at 2, 5.

¹⁵² Medin Opening Report, ¶ 133.

¹⁵³ ’319 Patent Publication, ¶ 84-85.

obvious Claim 8 of the '388 Patent. Here, Claim 8 is directed to a new and novel treatment using that compound, rather than to the compound itself. In my opinion, paragraphs 84-85 of the '319 Patent Publication do not disclose or render obvious claim 8, a novel method of treating a subset of Fabry patients with certain α -Gal A mutations.

139. Dr. Medin also relies on Proposed Claim 10 of the '319 Patent Publication, which states:

10. A method of treating a patient diagnosed with Fabry disease which comprises administering to the patient a therapeutically effective dose of 1-deoxygalactonorjirimycin, wherein the patient expresses a mutant α -galactosidase A selected from the group consisting of the α -galactosidase A mutations A257D, A257G, A257P, A291T, A292T, A307T, **A309P**, **A352V**, A368T, A73V, A97V, C174G, C174R, C56F, C56Y, D165H, D313G, D322E, D55V, E203V, F169S, G171R, G183A, G183V, G258R, G258V, G261D, G325S, G360D, G360S, G85D, G85M, I117S, I198T, I239T, I253T, I289S, I319T, I359T, K185E, K308N, L166G, L16H, L19P, L243W, L36F, L36S, L372P, L403S, L54P, M290I, M290L, M296L, M296T, M42L, M42R, M76T, M96I, N53L, P205S, P293T, P409A, P409T, P60L, Q107L, Q250P, Q312R, Q321H, Q321L, R301G, **R356G**, S238N, S247C, T282A, T410I, V339E, W162G, W349S, Y152C, Y184C, Y200C, Y207H and Y216C.¹⁵⁴

From this list of over eighty mutations, Dr. Medin then focuses on only a few cherry-picked mutations based on their amino acid positions.¹⁵⁵ While Claim 8 of the '388 Patent does include mutations at positions 309, 352, and 356 (specifically A309**V**, A352**G**, and R356**P**), the mutations are different from those in Proposed Claim 10 of the '319 Patent Publication.

140. Similarly, Dr. Medin also opines that the '319 Patent Publication “discloses that the mutations A20P, I242N, A309P, A352V, R356G, and R356W are responsive to migalastat, i.e., they are HEK assay amenable mutations.”¹⁵⁶ Dr. Medin then opines that “a [person of ordinary skill in the art] would know that amino acid positions 20, 242, 309, 352, and 356 on α -

¹⁵⁴ '319 Patent Publication, Proposed Claim 10.

¹⁵⁵ Medin Opening Report, ¶ 127 (calling attention to A309P, A352V, and R356G).

¹⁵⁶ Medin Opening Report, ¶ 131, Ex. C at 2-4, 5-6.

galactosidase A have missense mutations in Fabry patients and would therefore be motivated to explore other mutations at the same amino acid positions.”¹⁵⁷

141. As a preliminary matter, Dr. Medin seems to be mixing up the concepts of responsiveness in the HEK assay described in the ’319 Patent Publication with the concept of HEK assay amenable mutations described in the ’388 Patent. In drawing this inappropriate parallel, Dr. Medin is using the ’388 Patent’s disclosures and thus is using hindsight to support his obviousness arguments. The assay in the ’319 Patent Publication is different than the assay in the ’388 Patent and Claim 8 refers to a “HEK assay amenable mutation” in the Migalastat Amenability Assay—the assay described in the ’388 Patent, not the assay described in the ’319 Patent Publication.

142. Further, I disagree with Dr. Medin’s opinions for several other reasons. *First*, as described above in the technology background (§VI), Fabry disease is difficult to diagnose and treat because there are many different α -Gal A mutations that cause Fabry disease. Each mutation may cause different symptoms, ultimately causing different presentations of the disease in each patient. A disclosure that a patient with one of the α -Gal A mutations, for example, as in Proposed Claim 10 of the ’319 Patent Publication, could be treated with migalastat does not inform a person of ordinary skill in the art whether other Fabry disease patients with different α -Gal A mutations could be treated with migalastat. Further, the ’319 Patent Publication discloses examples of an α -Gal A mutation at a specific amino acid location being responsive to treatment with migalastat and a different mutation at the same location is not.¹⁵⁸ In fact, the ’319 Patent

¹⁵⁷ Medin Opening Report, ¶ 131.

¹⁵⁸ ’319 Patent Publication, at Fig. 17 (showing responsive GLA mutations L16H, N34K, R112H, N224S, A352V); ’319 Patent Publication, Fig. 18 (showing non-responsive GLA mutations L16P, N34S, R112C, R112S, N224D, A352P, A352D).

Publication itself recognizes that there is no way to predict whether a Fabry patient with a specific mutation will be responsive or not to treatment with migalastat prior to testing.¹⁵⁹ This remains true even if the mutation occurs at the same position in the α -Gal A protein. For example, the '319 Patent Publication discloses that the L16H, N34K, R112H, N224S, A352V mutations are responsive to treatment with migalastat but the L16P, N34S, R112C, R112S, N224D, A352P, A352D mutations are non-responsive to treatment with migalastat.¹⁶⁰ Thus, a person of ordinary skill in the art would not be motivated based on the disclosures of the '319 Patent Publication to look for other α -Gal A mutations at the same amino acid position as a mutation that is reported as responsive to treatment with migalastat in the '319 Patent Publication. The '319 Patent Publication, including Proposed Claim 10, does not include any of the α -Gal A mutations in Claim 8 of the '388 Patent and therefore does not disclose or render obvious treatment of Fabry patients with the specific α -Gal A mutations of Claim 8 with migalastat. Just because a specific mutation at a particular amino acid position results in an α -Gal A protein that is responsive to treatment with migalastat as measured by the HEK assay discussed in the '319 Patent Publication does not allow a person of ordinary skill in the art to predict which other mutations at the same amino acid position may be responsive.

143. ***Second***, none of the A20P, I242N, A309P, A352V, R356G, and R356W mutations are included in Claim 8. There is no other reason Dr. Medin points to that would lead a person of ordinary skill in the art to treat Fabry patients with one of the specific mutations in

¹⁵⁹ '319 Patent Publication, ¶ 0150 (“DGJ-responsive and non-responsive mutant forms did not appear to be located to particular regions or domains on the α -Gal A protein structure.”); '319 Patent Publication, ¶ 0146 (“No significant correlation between response and location on the protein sequence of a mutation was observed, suggesting that responsive as well as non-responsive mutations are distributed widely across the entire protein.”).

¹⁶⁰ '319 Patent Publication, at Figs. 17-18.

Claim 8 with migalastat based on the disclosure in the '319 Patent Publication that different mutations are responsive to treatment with migalastat.

144. **Third**, the '319 Patent Publication discloses that some α -Gal A mutations are responsive to treatment with migalastat and some are not.¹⁶¹ In addition, the '319 Patent Publication references hundreds of missense mutations and there are many different positions for possible mutations. Dr. Medin cherry picks these amino acid positions for a select few of the hundreds of mutations based on hindsight. Dr. Medin presents no reason why a person of ordinary skill in the art would look to these few mutations rather than the hundreds of others in the '319 Patent Publication.

145. Further, Dr. Medin also opines that the '319 Patent Publication “discloses that the α -galactosidase A mutations A13P, Q57L, P146S, and I242F were generated by site-directed mutagenesis.”¹⁶² Further, Dr. Medin opines that “[t]he specification of the '388 Patent identifies [the A13P, Q57L, P146S, and I242F] mutations as HEK assay amenable mutations.”¹⁶³ This, however, is misleading because the '319 Patent Publication identifies each of these four mutations as non-responsive.¹⁶⁴ In my opinion, Dr. Medin is using hindsight, and the teachings of the '388 Patent, for his obviousness analysis with respect to Claim 8 of the '388 Patent. Further, I understand that the disclosures of the '388 Patent on these four mutations being amenable should not be used to support the proposition that the invention of the '388 Patent is obvious when the prior art discloses that these mutations are non-amenable.

¹⁶¹ '319 Patent Publication, at Figs. 17-18.

¹⁶² Medin Opening Report, ¶ 132 (citing '319 Patent Publication, Fig. 1A).

¹⁶³ Medin Opening Report, ¶ 132.

¹⁶⁴ '319 Patent Publication, Figs. 1A, 18, ¶¶ 0026, 0043, 0177.

146. In fact, although the '319 Patent Publication discusses these four mutations, which appear in Claim 8 of the '388 Patent, the '319 Patent Publication discourages a person of skill in the art from treating Fabry patients with one of these mutations with migalastat. For example, for certain of these Fabry disease patients—those with an A13P, Q57L, P146S, or I242F mutation—the '319 Patent Publication discloses that such patients should not be treated with migalastat, because according to the results obtained by the HEK assay described in the '319 Patent Publication, these mutations are non-responsive to treatment with migalastat.¹⁶⁵ The '319 Patent Publication discloses—based on the results of the in vitro activity assay described in the '319 Patent Publication—that Fabry patients with an A13P, Q57L, P146S, or I242F mutation are non-responsive to migalastat.¹⁶⁶ For example, the '319 Patent Publication discloses that each of the A13P, Q57L, P146S, and I242F mutations is a “[n]on-responsive GLA mutation[.]”¹⁶⁷ The '319 Patent Publication also teaches that Fabry patients with non-responsive α -Gal A mutations should not be treated with migalastat.¹⁶⁸ The '319 Patent Publication states:

In a further embodiment, the invention relates to a method of treating a patient diagnosed with Fabry disease by administering to the patient a therapeutically effective dose of 1-deoxygalactonorigirimycin, or a similar pharmacological chaperone to a patient that expresses a mutation in α -galactosidase A, ***with the proviso that the mutation is not a nonresponsive mutation*** and/or the mutation is not a mutation in which no enzyme is expressed.¹⁶⁹

In my opinion, a person of ordinary skill in the art would not be motivated to treat Fabry disease patients with one of the mutations A13P, Q57L, P146S, or I242F based on the disclosures of the

¹⁶⁵ '319 Patent Publication, at Figs. 1A, 18, ¶¶ 0026, 0043, 0177.

¹⁶⁶ '319 Patent Publication, at Fig. 18.

¹⁶⁷ '319 Patent Publication at Figs. 1A, 18, ¶¶ 0026, 0043, 0177.

¹⁶⁸ '319 Patent Publication, ¶ 0177.

¹⁶⁹ '319 Patent Publication, ¶ 0025 (emphasis added).

'319 Patent Publication. Rather, the '319 Patent Publication discourages a skilled artisan, or teaches away, from treating such Fabry patients with migalastat.

147. A person of ordinary skill in the art would know that treating Fabry patients with α -Gal A mutations that are non-responsive to migalastat is not the most beneficial treatment for a patient and a person of ordinary skill in the art would not be motivated to treat patients with non-responsive mutations with migalastat and would not have a reasonable expectation of success in doing so. Further, it would be unethical for a physician to treat a patient with a drug that the physician knows is not the optimal drug for that patient, and thereby prevent them from receiving the most beneficial treatment for their specific disease. Dr. Medin fails to acknowledge further prior art references that suggest treating a Fabry patient who has a non-amenable mutation with migalastat would not be beneficial. Thus, it is my opinion that Dr. Medin fails to provide any reason why a person of ordinary skill in the art would be motivated to treat such Fabry patients with a reasonable expectation of success upon reading the '319 Patent Publication. Dr. Medin also fails to provide any reason why a person of ordinary skill in the art would be motivated to search for a different answer than the one provided in the '319 Patent Publication on whether a Fabry patient with an A13P, Q57L, P146S, or I242F mutation would respond to treatment with migalastat.

148. In addition, the '319 Patent Publication does not disclose the other specific mutations of Claim 8 of the '388 Patent—namely, A20D, G80D, D175E, K213M, M267T, A309V, V316I, V316G, P323R, A352G, R356P, T385A, V390M, and G395A—and likewise does not disclose methods of treatment for such Fabry patients. If a person of ordinary skill in the art were to look for whether any of these specific mutations had been tested in an in vitro HEK assay, he or she would have found the work of Lukas et al. Lukas et al. tested each of these

specific mutations in an in vitro HEK assay and found each to be non-responsive to treatment with migalastat.¹⁷⁰ Thus, in my opinion, a person of ordinary skill in the art would still not have been motivated to treat Fabry patients with any of these mutations with migalastat and certainly would not have had a reasonable expectation of success in doing so.

149. Dr. Medin further opines that “[a]s being HEK assay amenable is an inherent property of the identified mutations, this claim limitation would have inherently existed in the prior art.”¹⁷¹ It is not clear to me what Dr. Medin is suggesting. As already discussed, none of the prior art that Dr. Medin relies upon teaches the HEK assay of the ’388 Patent; nor do they, either alone or in combination, teach that a Fabry patient with any of the specific mutations of Claim 8 of the ’388 Patent may be amenable to migalastat treatment. To the contrary, the explicit teachings of the ’319 Patent Publication that the A13P, Q57L, P146S, and I242F mutations are “non-responsive” to treatment with migalastat and that other prior art (e.g., Lukas et al.) that disclosed the remaining mutations in Claim 8 as non-responsive to treatment with migalastat would have taught a skilled person in the art away from using migalastat for treating these patients.

150. Dr. Medin opines that “[a] [person of ordinary skill in the art] would have been motivated to identify patients with GLA mutations suffering from Fabry disease, determine if these mutations are HEK amenable mutations, and once a mutation such as A13P, Q57L, P146S, or I242F, would be determined to be an HEK assay amenable mutation, to administer migalastat

¹⁷⁰ Jan Lukas et al., *Functional and Clinical Consequences of Novel α -Galactosidase A Mutations in Fabry Disease*, Human Mutation, Vol. 00, No. 0, 1–9 (2015) (ATGAL_00730664); Jan Lukas et al., *Functional Characterisation of Alpha-Galactosidase A Mutations as a Basis for a New Classification System in Fabry Disease*, PLOS Genetics, Vol 9, Issue 8 (Aug. 2013) (ATGAL_09916904 at -910; ATGAL_01136145).

¹⁷¹ Medin Opening Report, ¶ 132.

to patients having these mutations.”¹⁷² For the reasons explained above, I also disagree with this opinion. For example, with respect to the specific mutations in Claim 8 of the ’388 Patent, a person of ordinary skill in the art using the HEK assay described in the ’319 Patent Publication would have found each of A13P, Q57L, P146S, and I242F to be non-responsive to migalastat and thus would not have been motivated to treat such patients with migalastat with any reasonable expectation of success. Similarly, to the extent a person of ordinary skill in the art was to look for whether one of the other mutations in Claim 8 are responsive or non-responsive, such person of ordinary skill in the art would have found the work of Lukas et al., determined that such mutations were non-responsive to migalastat, and thus would not have been motivated to treat such patients with migalastat with any reasonable expectation of success. Dr. Medin has provided no reason why a person of ordinary skill in the art would have re-tested those mutations, much less how the mutations may be re-tested, or why they would have had a reasonable expectation of success in treating patients with the mutations in Claim 8 with migalastat. In addition, the ’319 Patent Publication discusses a HEK assay that was found to be unreliable in identifying Fabry patients who could benefit from treatment with migalastat. The inability of the assay discussed in the ’319 Patent Publication to accurately predict whether a mutation was responsive or non-responsive to migalastat was demonstrated by the failure to reach the primary endpoint in the six-month data for Amicus’s phase 3 clinical trial, which used this assay for enrollment.

151. Dr. Medin then opines that “claims 1 and 8 would have been obvious over the ’319 patent publication and the knowledge of a [person of ordinary skill in the art].”¹⁷³ As an

¹⁷² Medin Opening Report, ¶ 133 (citing ’319 Patent Publication, Fig. 1A), Ex. C at 2-3, 5-6.

¹⁷³ Medin Opening Report, ¶ 133; Ex. C at 2-3, 5-6.

initial matter, Dr. Medin did not identify this alleged combination in the summary of his opinions (Medin Opening Report, ¶ 13), and it is unclear if Dr. Medin is asserting this as a standalone combination. Further, I understand from counsel that Claim 1 is not asserted, and I have been asked to respond only as to Claim 8. With respect to Claim 8, I disagree. In my opinion, the disclosures of the '319 Patent Publication and the knowledge of a person of ordinary skill in the art do not render obvious Claim 8. Further, although Dr. Medin refers to the '319 Patent Publication in combination with the knowledge of a person of ordinary skill in the art, Dr. Medin does not identify any “knowledge of a [person of ordinary skill in the art]” that he is using as part of the obviousness analysis in this claim. Thus, in my opinion, Dr. Medin has failed to show that Claim 8 of the '388 Patent is obvious over the '319 Patent Publication in combination with the knowledge of a person of ordinary skill in the art. Dr. Medin generally fails to acknowledge the fact that the prior art references he relies on do not disclose treating Fabry patients with the specific mutations in Claim 8 and he fails to explain how a person of ordinary skill in the art would reach such a method of treatment for those specific mutations based on the references he relies upon, why a person of ordinary skill in the art would combine them, and why such a person would have a reasonable expectation of success in doing so.

b) Asserted Combination 2: Wu, Germain 2012, Giugliani, and/or Benjamin 2016 and the Knowledge of a Person of Ordinary Skill in the Art;

and

Asserted Combination 3: Wu and/or Germain 2012 in View of Benjamin 2016 and/or Giugliani and the Knowledge of a Person of Ordinary Skill in the Art

152. With respect to the vague combinations of Wu, Germain 2012, Giugliani and/or Benjamin in view of the knowledge of a person of ordinary skill in the art, and Wu and/or Germain 2012 in view of Benjamin 2016 and/or Giugliani and the knowledge of a person of

ordinary skill in the art, Dr. Medin opines that a person of ordinary skill in the art “would have been motivated to treat Fabry disease in a human patient by administering migalastat or a salt thereof.”¹⁷⁴ Dr. Medin claims that this motivation is supported by disclosures from Wu, Germain 2012, Giugliani, and Benjamin 2016.¹⁷⁵ I disagree. As a preliminary matter, a person of ordinary skill in the art would have understood from earlier prior art disclosures like the ’319 Patent Publication that not all Fabry patients can or should be treated by administration of migalastat or a salt thereof.¹⁷⁶

153. Dr. Medin opines that the motivation to treat Fabry disease by administration of migalastat or a salt thereof can be found in Wu’s disclosures that “migalastat hydrochloride (AT1001, GR181413A) migalastat [is] currently in clinical development to evaluate its safety and efficacy as a potential treatment for Fabry disease” and that “AT1001 (migalastat hydrochloride, 1-deoxygalactonojirimycin) is a pharmacological chaperone for α -Gal A that is in Phase 3 clinical development as a potential therapy for Fabry disease.”¹⁷⁷ I disagree because Dr. Medin overreads Wu. Wu’s teachings are directed to a certain subset of Fabry patients rather than all Fabry patients, and certainly not all Fabry patients with amenable mutations. For example, Wu states that “a pharmacological chaperone may be a viable treatment for Fabry disease, serving as an alternative to enzyme replacement therapy *for some patients*.”¹⁷⁸ Wu also recognizes that not all Fabry patients benefit from treatment with migalastat.¹⁷⁹ Wu also

¹⁷⁴ Medin Opening Report, ¶ 128; Ex. C at 2-3, 5-6.

¹⁷⁵ Medin Opening Report, ¶ 128; Ex. C at 2-3, 5-6.

¹⁷⁶ ’319 Patent Publication, ¶¶ 0025, 0177.

¹⁷⁷ Medin Opening Report, ¶ 128 (quoting Wu at 965, 974); Ex. C at 2, 5.

¹⁷⁸ Wu at 965 (emphasis added).

¹⁷⁹ Wu at 975.

discloses that “[f]urther evaluation of the utility of the HEK-293 cell-based assay for Fabry patient selection for treatment with AT1001 [migalastat hydrochloride] is ongoing.”¹⁸⁰ In my opinion, a skilled artisan would understand this disclosure to mean that Wu is limited to specific Fabry patients in certain of Amicus’s phase 2 clinical trials.¹⁸¹ In addition, although Wu mentions Phase 3 clinical trials, it does not disclose what mutations are being studied in those trials, or whether any such mutations can be treated with migalastat. Further, a skilled artisan would have understood that the initial data from those phase 3 clinical studies was reported by Amicus as “not meet[ing] statistical significance.”¹⁸² As such, Wu does not provide reliable methods of treating Fabry patients, even for the mutations explicitly discussed in the reference, and the disclosures cannot be used to extrapolate any methods of treatment for Fabry patients who are not discussed in the reference. Thus, it is my opinion that Wu does not provide any teaching on how to treat Fabry patients with the α -Gal A mutations from Claim 8.

154. Next, Dr. Medin opines that the motivation to treat Fabry disease by administration of migalastat or a salt thereof can be found in Germain 2012’s disclosure that “[m]igalastat HCl is a candidate pharmacological chaperone that provides a novel genotype-specific treatment for [Fabry disease].”¹⁸³ I disagree. Even this disclosure recognizes that the treatment would be “genotype-specific” and thus cannot be applied to all Fabry patients. This is because Germain 2012 discloses results from only a limited number of Fabry patients with

¹⁸⁰ Wu at 976.

¹⁸¹ Wu at Table 2 (discussing FAB-CL-201, FAB-CL-202, and FAB-CL-203 trial data).

¹⁸² Amicus Website, Press Release dated Feb. 15, 2013, available at <https://ir.amicusrx.com/news-releases/news-release-details/amicus-therapeutics-presents-additional-6-month-results-phase-3>.

¹⁸³ Medin Opening Report, ¶ 128 (quoting Germain 2012, Abstract); Ex. C at 2, 5.

specific mutations, none of which overlap with those in Claim 8.¹⁸⁴ As such, a person of ordinary skill in the art would understand that certain patients would not benefit from treatment with migalastat hydrochloride. Absent specific disclosure that a patient with a specific mutation would benefit from migalastat treatment, a skilled artisan would not be motivated to treat such patients with migalastat. Thus, it is my opinion that Germain 2012 does not provide any teaching on how to treat Fabry patients with the disclosed α -Gal A mutations of Claim 8 of the '388 Patent.

155. Dr. Medin also opines that the motivation to treat Fabry disease by administration of migalastat or a salt thereof can be found in Giugliani's disclosure of the "evaluation of 'the safety and pharmacodynamics of migalastat hydrochloride, an investigational pharmacological chaperone given orally every other day (QOD) to females with FD.'" ¹⁸⁵ I disagree. Giugliani discloses specific results related to "nine females with [Fabry disease]." ¹⁸⁶ As such, a person of ordinary skill in the art would not understand such disclosure could be expanded to all Fabry disease patients, regardless of their specific α -Gal A mutations. Thus, it is my opinion that Giugliani does not provide any teaching on how to treat Fabry patients with the α -GAL A mutations from Claim 8.

156. Lastly, Dr. Medin opines that the motivation to treat Fabry disease by administration of migalastat or a salt thereof can be found in Benjamin 2016 because it "discloses the administration of migalastat HCl to treat Fabry Disease patients." ¹⁸⁷ I disagree.

¹⁸⁴ Germain 2012 at Abstract (describing results from two phase 2 studies of nine males with Fabry disease).

¹⁸⁵ Medin Opening Report, ¶ 128 (quoting Giugliani, Abstract); Ex. C at 2, 5.

¹⁸⁶ Giugliani at Abstract.

¹⁸⁷ Medin Opening Report, ¶ 128 (citing Benjamin 2016 at 2); Ex. C at 2, 5.

Benjamin 2016 does not provide any information on any specific α -GAL A mutations, or which mutations are amenable to treatment with migalastat. Without this information, a person of ordinary skill in the art would not be motivated to treat Fabry patients generally with migalastat. This is especially the case because Benjamin 2016 confirms that migalastat cannot be used for all Fabry patients, and thus mutation-specific treatment is required.¹⁸⁸ Thus, it is my opinion that Benjamin 2016 does not provide any teaching on how to treat Fabry patients with the α -GAL A mutations from Claim 8 of the '388 Patent.

157. With respect to these claim limitations, Dr. Medin opines that “it was well known that a HEK-293 cell-based assay could be used to identify mutant forms of α -Gal A that are responsive to migalastat” and points to disclosures in Germain 2012, Wu, Benjamin, and Giugliani.¹⁸⁹ In my opinion, this is not an accurate description of the state of the field at the time of the invention of Claim 8 of the '388 Patent. Wu, Germain 2012, and Giugliani disclose a research-based HEK assay. Benjamin, on the other hand, discusses the development of another HEK assay. Dr. Medin is conflating these two distinct assays in his analysis. The HEK-293 cell-based assay used in Germain 2012, Wu, and Giugliani could not accurately predict whether a mutation was responsive or non-responsive to migalastat and the disclosures in Benjamin do not identify to a person of ordinary skill in the art which mutations are being discussed with respect to the Migalastat Amenability Assay.¹⁹⁰ The inability of the assay discussed in Germain 2012, Wu, and Giugliani to accurately predict whether a mutation was responsive or non-

¹⁸⁸ Benjamin 2016, at 2 (“30-50% of patients with [Fabry Disease] are estimated to have amenable mutations”).

¹⁸⁹ Medin Opening Report, ¶¶ 134-135.

¹⁹⁰ See generally Benjamin 2016.

responsive to migalastat was demonstrated by the failure to reach the primary endpoint in the six-month data for Amicus's phase 3 clinical trial, which used this assay for enrollment.

158. Dr. Medin opines that "Germain 2012 also discloses α -galactosidase A mutations that cause Fabry disease."¹⁹¹ This vastly overstates Germain 2012's disclosures because Germain 2012 merely relates to nine male Fabry disease patients with eight unique α -Gal A mutations, none of which are disclosed in Claim 8 of the '388 Patent. As noted above, Germain 2012 refers to the HEK assay that was determined to be unreliable, including because it was used for enrollment in Amicus's phase 3 clinical studies, which resulted in the 011 study failing to meet its endpoint for the first six months of data.

159. Dr. Medin also points to Germain 2012's disclosures that "[a]n in vitro α -Gal-A gene transfection assay, specific for each individual mutation, was developed in HEK-293 cells" and that this was "used to define if a patient carrying a GLA mutation was amenable to migalastat HCl;" and Dr. Medin asserts that "Germain 2012 further discloses mutations considered amenable to migalastat HCl."¹⁹² In my opinion, Dr. Medin is ignoring the context of such disclosures and, as a result, is vastly overstating Germain 2012's disclosures. The HEK-293 cell-based assay discussed in Germain 2012 could not accurately predict whether a mutation is amenable to migalastat. Further, Germain 2012 only relates to nine male Fabry patients, with eight unique mutations, none of which are in Claim 8 of the '388 Patent and Germain 2012 notes that the HEK assay testing was done retrospectively. Germain 2012 does not disclose all mutations considered amenable to migalastat nor does it disclose a reliable way to identify all

¹⁹¹ Medin Opening Report, ¶ 138 (citing Germain 2012 at 3, 5, 9).

¹⁹² Medin Opening Report, ¶ 134 (citing Germain 2012 at Abstract, 4-5); Ex. C at 2, 5.

such mutations. Thus, it is my opinion that Germain 2012 does not provide any teaching on the α -Gal A mutations from Claim 8 of the '388 Patent.

160. Dr. Medin opines that “Wu also states that α -galactosidase A mutations that cause Fabry disease.”¹⁹³ It is not clear what Dr. Medin means by this. Dr. Medin also points to Wu’s disclosure of a “cell-based assay in cultured HEK-293 cells to identify mutant forms of α -GAL-A that are responsive to [migalastat HCl].”¹⁹⁴ The HEK-293 cell-based assay in Wu was found to be unreliable in identifying responsive and non-responsive mutations. Further, Wu only discloses data for a limited number of specific mutations from in vitro testing and none of those mutations are in Claim 8 of the '388 patent. Dr. Medin also opines that “Wu discloses the α -galactosidase A HEK 293 assay amenable mutation Q57L.”¹⁹⁵ I disagree. Wu does not disclose whether Q57L is responsive or non-responsive to migalastat. Rather, Wu discloses that the double missense mutation, D55V/Q57L, is responsive to migalastat according to the in vitro HEK assay described in Wu. Specifically, Wu’s Table 1 that Dr. Medin relies on gives results related to the double missense mutation D55V/Q57L, not to the single missense mutation Q57L, as shown below.¹⁹⁶

¹⁹³ Medin Opening Report, ¶ 137 (citing Wu at 969-70, Table 1); Ex. C at 2, 5.

¹⁹⁴ Medin Opening Report, ¶ 134 (quoting Wu at Abstract); Ex. C at 2, 5.

¹⁹⁵ Medin Opening Report, ¶ 138 (citing Wu at 969-70 (Table 1)); Ex. C at 2, 5.

¹⁹⁶ Wu at Table 1 (excerpted and annotated).

Table 1. Continued

Protein change	cDNA change	[AT100]		[AT100]		Relative increase	EC ₅₀ (μM)	n
		α-Gal A Activity	% WT	α-Gal A Activity	% WT			
p.G325D	c.974G>A	0.0 ± 0.0	0.0 ± 0.0	8,439 ± 1,441***	26.2 ± 7.2	NC	430 ± 144*	3
p.G328A	c.983G>C	1,320 ± 136	3.9 ± 0.1	26,534 ± 718***	79.0 ± 5.7	21.0 ± 1.9	31.3 ± 3.8	3
p.R342Q	c.1025G>A	0.0 ± 0.0	0.0 ± 0.0	1,175 ± 137*	4.4 ± 0.4	NC	95.0 ± 39.3	4
p.R356W	c.1066C>T	2,352 ± 276	7.6 ± 1.4	23,720 ± 2,474*	75.6 ± 11.6	10.1 ± 1.3	5.4 ± 0.6	3
p.E358A	c.1073A>C	639 ± 200	1.8 ± 0.4	8,680 ± 902**	26.9 ± 4.2	16.0 ± 4.4	16.4 ± 5.4	4
p.E358K	c.1072G>A	0.0 ± 0.0	0.0 ± 0.0	1,417 ± 136*	3.7 ± 0.5	NC	281 ± 32	4
p.R363C	c.1087C>T	2,385 ± 119	7.5 ± 0.7	13,603 ± 1,559*	42.0 ± 3.9	5.5 ± 0.4	3.7 ± 0.3	3
p.R363H	c.1088G>A	8,302 ± 2,086	24.1 ± 6.8	25,721 ± 2,292**	73.4 ± 5.3	3.3 ± 0.5	16.7 ± 6.5	4
p.P409A	c.1225C>G	834 ± 116	2.8 ± 0.5	12,572 ± 2,254*	42.0 ± 7.8	15.3 ± 1.6	11.3 ± 1.9	3
p.L415P	c.1244T>C	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	NC	NC	7
p.D55V/Q57L	c.164A>T/170C>T	0.0 ± 0.0	0.0 ± 0.0	5,557 ± 800*	16.9 ± 1.9	NC	29.4 ± 10.8	4
p.L120P/AT21T	c.359T>C/361G>A	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	NC	NC	4

In my opinion, whether a double missense mutation is responsive to migalastat is not predictive of whether either of the single missense mutations will be responsive to migalastat.¹⁹⁷ Thus, in my opinion, a person of ordinary skill in the art would not understand Wu to disclose Q57L as responsive to migalastat. Claim 8 does not include the double missense mutation D55V/Q57L and, therefore, Dr. Medin’s reliance on the disclosures in Wu Table 1 is misplaced. I understand that Dr. Elfrida Benjamin testified that knowledge of the responsiveness of a double mutation like D55V/Q57L does not allow a person of ordinary skill in the art to predict how the single mutation Q57L would behave.¹⁹⁸ Thus, it is my opinion that Wu does not provide any teaching on the α-Gal A mutations from Claim 8 of the ’388 Patent.

161. Dr. Medin cites Giugliani’s disclosure that “[p]atients with amenable mutations seemed to demonstrate greater pharmacodynamic response to migalastat HCl compared to patients with non-amenable mutations.”¹⁹⁹ Dr. Medin also opines that “Giugliani further discloses, ‘migalastat HCl was generally well tolerated and, in patients with amenable mutations,

¹⁹⁷ ’319 Patent Publication, Figs. 17, 18 (showing D264Y and V269M are each individually responsive but double mutation D264Y/V269M is not responsive).

¹⁹⁸ See, e.g., E. Benjamin Dep. Tr. 107:4–12, 117:1–9.

¹⁹⁹ Medin Opening Report, ¶ 136 (quoting Giugliani at Abstract); Ex. C at 2, 5.

resulted in GL-3 substrate reduction in urine and some kidney cell types.”²⁰⁰ Dr. Medin is taking these disclosures out of context and overstates Giugliani’s disclosures. Giugliani’s disclosures relate to limited results of nine female Fabry disease patients with eight unique α -Gal A mutations (four responsive and four non-responsive) who were enrolled in Phase 2 clinical trials with different dose regimens of migalastat hydrochloride.²⁰¹ In my opinion, this limited data cannot be extrapolated to a general statement that all Fabry patients with amenable mutations demonstrate greater pharmacodynamic response to migalastat hydrochloride compared to Fabry patients with non-amenable mutations. Dr. Medin also opines that “Giugliani further discloses categorizing GLA mutations ‘as being amenable or not to migalastat HCl based on an in vitro α -Gal A transfection assay developed in human embryonic kidney (HEK)-293 cells.”²⁰² Like Germain 2012 and Wu, Giugliani refers to a HEK-293 cell-based assay that was determined to be unreliable at identifying responsive and non-responsive mutations; and further, the assay results as to amenability are only disclosed for the eight mutations at issue in the study, and not generally for all Fabry mutations. None of the eight mutations in the study appears in Claim 8 of the ’388 patent. In addition, Giugliani refers to the HEK assay that was determined to be unreliable, including because it was used for enrollment in Amicus’s phase 3 clinical studies, which resulted in the 011 study failing to meet its endpoint for the first six months of data. Thus, it is my opinion that Giugliani does not provide any teaching on the α -Gal A mutations from Claim 8 of the ’388 Patent.

²⁰⁰ Medin Opening Report, ¶ 136 (quoting Giugliani at Abstract, 91); Ex. C at 2, 5.

²⁰¹ Giugliani at Abstract, Table 2.

²⁰² Medin Opening Report, ¶ 136 (quoting Giugliani at Abstract); Ex. C at 2, 5.

162. Dr. Medin’s reliance on Benjamin 2016 is equally misplaced. Dr. Medin opines that “Benjamin (2016) discloses the identification of amenable mutant forms of α -Gal A using a GLP-validated HEK-293 cell-based assay (Migalastat Amenability Assay) and that ‘the Migalastat Amenability Assay and amenable mutation criteria have high predictive value in identifying [Fabry Disease] patients who show a pharmacodynamic response to oral administration of migalastat.’”²⁰³ I disagree. In my opinion, Benjamin 2016 does not disclose the identification of amenable mutant forms of α -Gal A using the Migalastat Amenability Assay. Notably, there are no specific mutations mentioned at all on the page that Dr. Medin cites, or anywhere in the poster.²⁰⁴ In my opinion, the disclosure that the Migalastat Amenability Assay is highly predictive of pharmacodynamic response to oral administration of migalastat does not provide a person of ordinary skill in the art with a motivation to treat any specific Fabry disease patient with migalastat. In addition, Benjamin 2016 does not disclose treatment of Fabry patients with any of the specific mutations in Claim 8. Thus, it is my opinion that Benjamin 2016 does not provide any teaching on the α -Gal A mutations from Claim 8 of the ’388 Patent.

163. Dr. Medin next opines that “[i]t was known that mutations in the GLA gene that encode α -galactosidase A (α -Gal A) cause Fabry disease,” and that “[b]y 2011, more than 600 disease-causing mutations in the GLA gene had been identified . . . and by March 2016, more than 800 disease-causing mutations in the GLA gene had been identified”²⁰⁵ In my opinion, the high number of unique GLA mutations that had been discovered adds to the complexity of the methods of treatment with migalastat and supports the nonobviousness of Claim 8. In my

²⁰³ Medin Opening Report, ¶ 135 (citing Benjamin 2016 at 7); Ex. C at 2, 5.

²⁰⁴ Benjamin 2016 at 7.

²⁰⁵ Medin Opening Report, ¶ 139.

opinion, it would not have been obvious to try treatment with migalastat for Fabry patients with the specific mutations of Claim 8 of the '388 Patent, especially given the unpredictability of whether or not Fabry patients with a given mutation would respond to treatment with migalastat; further, a person of ordinary skill in the art would not have had a reasonable expectation of success with respect to treating Fabry patients that carry the specific mutations of Claim 8 with migalastat.

164. Dr. Medin opines that “[i]t was well known that migalastat selectively binds and stabilizes α -Gal A, and that a HEK-293 cell-based assay could be used to identify mutant forms of α -Gal A that are responsive to migalastat.”²⁰⁶ Dr. Medin further opines that “[t]he prior art teaches the development of an oral therapy of migalastat HCl for the treatment of Fabry disease . . . and the use of a HEK-293 cell-based assay to identify patients with α -Gal A mutations that are amenable to migalastat treatment.”²⁰⁷ In my opinion, Dr. Medin has vastly overstated the state of the field at the time the application leading to the '388 Patent was filed. In fact, the HEK-293 cell-based assay from the '319 Patent Publication, Wu, Germain 2012, and Giugliani was found to be unable to accurately identify which patients to treat with migalastat. In addition, Benjamin 2016 did not disclose sufficient information about the Migalastat Amenability Assay to identify or determine which mutations are amenable to migalastat treatment. Further, Benjamin 2016 does not disclose treatment of Fabry patients with any of the specific mutations in Claim 8. Indeed, pharmacological chaperones were a relatively new avenue of treatment that was being explored. As of the priority date, there were no FDA approved pharmacological chaperones for

²⁰⁶ Medin Opening Report, ¶ 139.

²⁰⁷ Medin Opening Report, ¶ 140.

any disease, let alone for Fabry disease.²⁰⁸ Although there were theories about how migalastat may be able to selectively bind and stabilize α -Gal A in certain situations, it was unknown when this would occur; and the disclosures in the art at the time suggested that it was highly unpredictable which mutated α -Gal A would be stabilized by migalastat. Further, the HEK assay referred to in those references was determined to be unreliable, including because it was used for enrollment in Amicus's phase 3 clinical studies, which resulted in the 011 study failing to meet its endpoint for the first six months of data.

165. Dr. Medin opines that "it would have been obvious for a [person of ordinary skill in the art] to simply carry out the steps of a known cell assay to identify the naturally-occurring α -galactosidase A mutations recited in at least claims 1 and 8."²⁰⁹ For all of the reasons discussed above, I disagree. Further, as I discussed above, all the mutations of Claim 8 were identified as non-responsive to migalastat in the prior art.²¹⁰ In addition, Wu, Germain 2012, and Giugliani would discourage a person of skill in the art from treating Fabry patients with one of

²⁰⁸ See e.g., Keyzor I., et al., (2023) Therapeutic Role of Pharmacological Chaperones in Lysosomal Storage Disorders: A Review of the Evidence and Informed Approach to Reclassification, *Biomolecules* **13**(8):1227 ("The term "pharmacological chaperone therapy" or "PCT" was first coined in 2000 to describe the category of exogenously administered small molecules that restore folding and trafficking defects of misfolded proteins in LSDs. The EMA approved the first commercially available PCT, migalastat (Galafold®; Amicus Therapeutics Inc., Philadelphia, PA, USA), in 2016, for long-term treatment of adults with Fabry disease who have an amenable mutation (i.e., a mutation that is responsive to treatment).") (internal citation omitted) (ATGAL_10161626 at -627); May 31, 2016, Amicus Therapeutics Announces European Commission Approval for Galafold™ (Migalastat) in Patients with Fabry Disease in European Union (ATGAL_07336052 at -052); Moran, N., (2018) FDA Approves Galafold, a Triumph for Amicus, *Nat. Biotech.* 36:91 (ATGAL_10161450 at -450).

²⁰⁹ Medin Opening Report, ¶ 140; Ex. C at 2-3, 5-6.

²¹⁰ '319 Patent Publication at Figs. 17 & 18; Jan Lukas et al., *Functional and Clinical Consequences of Novel α -Galactosidase A Mutations in Fabry Disease*, Human Mutation, Vol. 00, No. 0, 1–9 (2015) (ATGAL_00730664); Jan Lukas et al., *Functional Characterisation of Alpha-Galactosidase A Mutations as a Basis for a New Classification System in Fabry Disease*, PLOS Genetics, Vol 9, Issue 8 (Aug. 2013) (ATGAL_09916904 at -910; ATGAL_01136145).

the mutations in Claim 8 with migalastat, including because had a person of ordinary skill in the art used the assay discussed in these references to determine whether Fabry patients with the mutations in Claim 8 were responsive to treatment with migalastat, he or she would have found that those mutations are categorized as nonresponsive and therefore would not have been motivated to treat such Fabry patients with migalastat. As such, a person of ordinary skill in the art would have had no reason to re-test these mutations based on these prior art references, much less how to re-test these mutations in a different assay. Further, Dr. Medin points to no reason why a person of ordinary skill in the art would have found these mutations in particular and been motivated to re-test these mutations to treat patients with one of those mutations, or any reason why a person of ordinary skill in the art would have had a reasonable expectation of success in doing so. Moreover, I understand from counsel that Claim 1 is not asserted. I have therefore been asked to limit my response to Claim 8.

166. Dr. Medin opines that “[a] [person of ordinary skill in the art] would have been motivated with a reasonable expectation of success to combine the teachings of Wu, Germain 2012, Benjamin (2016), and/or Giugliani, at least because each is directed to the use of migalastat in the treatment of Fabry disease and/or the evaluation of mutations in the α -galactosidase A gene in patients with Fabry disease that inform treatment options for Fabry disease, including treatment with migalastat.”²¹¹ I disagree. In my opinion, a person of ordinary skill in the art would not have combined results or teachings from Benjamin 2016 with those of Wu, Germain 2012, and Giugliani to treat Fabry patients with the specific mutations of Claim 8 of the ’388 Patent because they would have no reason to do it. More importantly, even if a person of ordinary skill in the art did combine such references, such person of ordinary skill in

²¹¹ Medin Opening Report, ¶ 141; Ex. C at 2-3, 5-6.

the art would not be motivated to reach the invention claimed in Claim 8 with any reasonable expectation of success for all of the reasons described above, including, *e.g.*, because none of the mutations at issue in Claim 8 are disclosed in these references as being amenable to migalastat.

Dr. Medin also opines that “a [person of ordinary skill in the art] seeking to improve upon existing treatments of Fabry disease would have been motivated with a reasonable expectation of success to combine the disclosures of Wu, and/or Germain 2012 in view of Benjamin (2016) and/or Giugliani, and the knowledge of a person of ordinary skill in the art.”²¹² He also opines that “a [person of ordinary skill in the art] would have been motivated to combine the teachings of Wu, Germain 2012, Giugliani, and/or Benjamin (2016) because they all have complementary teachings and show consistent outcomes, therefore, a [person of ordinary skill] in the art would also have an expectation of success in doing so.”²¹³ I also disagree with these opinions.

Dr. Medin fails to explain exactly which disclosures of Wu, Germain 2012, Benjamin 2016, and Giugliani a person of ordinary skill in the art would combine and why there is a motivation to combine, and why doing so would result in a reasonable expectation of success. Simply saying they have “complementary teachings and show consistent outcomes” does nothing to explain why there would be a reasonable expectation of success. Moreover, although Dr. Medin mentions knowledge of a person of ordinary skill in the art, he fails to identify exactly what that knowledge is.

167. It is unclear what combination Dr. Medin is relying upon for his analysis of Claim 8. Because Dr. Medin’s obviousness combinations are unclear, I reserve the right to supplement my opinions based on any additional and/or clarifying opinions that Dr. Medin renders with

²¹² Medin Opening Report, ¶ 141; Ex. C at 2-3, 5-6.

²¹³ Medin Opening Report, ¶ 142; Ex. C at 2-3, 5-6.

respect to Claim 8. Further, Dr. Medin fails to identify what he is using as his base reference, how he is modifying it and what reference he is modifying it with, and why a person of ordinary skill in the art would be motivated to modify the reference or have had a reasonable expectation of success in such a combination. Dr. Medin more generally fails to explain how he is combining the prior art references and how and why, in his opinion, such references would cause a person of ordinary skill in the art to reach the claimed invention. In addition, he generally fails to acknowledge the fact that the prior art references he relies on do not disclose treating Fabry patients with the specific mutations in Claim 8, and that they suggest Fabry patients with the mutations in Claim 8 should not be treated with migalastat. Moreover, Dr. Medin fails to explain how a person of ordinary skill in the art would reach such a method of treatment for those specific mutations based on the references he relies upon.

168. Based on my review of the prior art references and the disclosures cited, in my opinion, Claim 8 is not obvious and there is no motivation to combine the references with any reasonable expectation of success in reaching the invention of Claim 8. For all the reasons discussed herein, in my opinion, Dr. Medin has failed to prove that Claim 8 is obvious. Dr. Medin generally fails to acknowledge the fact that the prior art references he relies on do not disclose treating Fabry patients with the specific mutations in Claim 8 and he fails to explain how a person of ordinary skill in the art would reach such a method of treatment for those specific mutations based on the references he relies upon, why a person of ordinary skill in the art would combine them, and why such a person would have a reasonable expectation of success in doing so.

2. Claim 36

169. Claim 36 (bolded below) depends from Claim 7, which depends from Claim 1. The claim language is:

1. A method of treating Fabry disease, the method comprising administering migalastat to a patient in need thereof, wherein the patient has an α -galactosidase A protein comprising a HEK assay amenable mutation selected from the group consisting of: A13P, A20D, Q57L, G80D, P146S, D175E, K213R, K213M, I242F, M267T, A309V, V316I, V316G, P323R, A352G, R356P, T385A, V390M, and G395A.

7. The method of claim 1, wherein the mutation is selected from the group consisting of: G80D, P146S, M267T, and R356P.

36. The method of claim 7, wherein the patient is administered about 150 mg of migalastat hydrochloride every other day.

170. Based on my review of Dr. Medin's report, it is unclear what combinations Dr. Medin asserts for Claim 36. Dr. Medin lists only the following combinations in the summary of his opinions:

- 1) The '319 patent publication in view of Lockhart '093 and the knowledge of a person of ordinary skill in the art;
- 2) Wu, Germain [2012], Benjamin 2016, and/or Giugliani and the knowledge of a person of ordinary skill in the art;
- 3) Wu and/or Germain [2012] in view of Benjamin 2016 and/or Giugliani and the knowledge of a person of ordinary skill in the art.²¹⁴

171. Regarding the first combination—the '319 Patent Publication in view of Lockhart '093 and the knowledge of a person of ordinary skill in the art—Dr. Medin did not identify what knowledge a person of ordinary skill in the art would have had that is relevant to this combination or why a person of ordinary skill in the art would have been motivated to use that knowledge to modify what is disclosed in the '319 Patent Publication in view of Lockhart '093.

172. Regarding the second combination—Wu, Germain 2012, Benjamin, and/or Giugliani, and the knowledge of a person of ordinary skill in the art—it is unclear exactly which

²¹⁴ Medin Opening Report, ¶ 13; Ex. C at 3-4, 6-7.

of those references he is combining and how those references are being combined. Dr. Medin discusses each of the four references individually before alleging in a conclusory fashion that they could be combined with no explanation of how they would be combined.²¹⁵ Dr. Medin again failed to identify what knowledge a person of ordinary skill in the art would have had that is relevant to this combination or why a person of ordinary skill in the art would have been motivated to use that knowledge to modify what is disclosed in the references cited by Dr. Medin.

173. Regarding the third combination—Wu and/or Germain 2012 in view of Benjamin 2016 and/or Giugliani and the knowledge of a person of ordinary skill in the art—it is unclear exactly which of those references he is combining and how those references are being combined. Like with the second combination, Dr. Medin discusses each of the four references individually before alleging in a conclusory fashion that they would be combined, with no explanation of how they would be combined or why a person of ordinary skill in the art would combine them.²¹⁶ Again, Dr. Medin failed to identify what knowledge a person of ordinary skill in the art would have had that is relevant to this combination or why a person of ordinary skill in the art would

²¹⁵ See Medin Opening Report, ¶ 150 (“In addition, a POSA [person of ordinary skill in the art] would have been motivated to combine the teachings of Wu, Germain [2012], Giugliani and/or Benjamin (2016) because they all have complementary teachings and show consistent outcomes. Therefore, a POSA [person of ordinary skill in the art] would also have an expectation of success in doing so.”); *see also* ¶ 149 (“A POSA [person of ordinary skill in the art] would have been motivated with a reasonable expectation of success to combine the teachings of Wu, Germain 2012, Benjamin (2016), and/or Giugliani, at least because each is directed to the use of migalastat in the treatment of Fabry disease and/or the evaluation of mutations in the α -galactosidase A gene in patients with Fabry disease that inform treatment options for Fabry disease, including treatment with migalastat.”).

²¹⁶ See Medin Opening Report, ¶ 149 (“Furthermore, a POSA [person of ordinary skill in the art] seeking to improve upon the existing treatments of Fabry disease would have been motivated with a reasonable expectation of success to combine the disclosures of Wu, and/or Germain 2012 in view of Benjamin (2016) and/or Giugliani, and the knowledge of a POSA [person of ordinary skill in the art].”).

have been motivated to use that knowledge to modify what is disclosed in the references cited by Dr. Medin.

174. In my opinion, as discussed further below, Dr. Medin's combinations do not disclose the limitations of Claim 36 and do not render Claim 36 obvious.

175. I incorporate by reference my analysis of the limitations in Claim 1 that I have discussed above with respect to Claim 8. I address the remaining limitations of Claim 36 below.

a) Asserted Combination 1: the '319 Patent Publication in view of Lockhart '093 and the Knowledge of a Person of Ordinary Skill in the Art

176. Claim 36 recites four specific mutations, G80D, P146S, M267T, and R356P. Dr. Medin opines that "[t]he '319 patent publication discloses that the α -galactosidase A mutations A13P, Q57L, P146S, and I242F were generated by site-directed mutagenesis."²¹⁷ But this is both confusing and misleading because in particular, although the '319 Patent Publication does discuss the four mutations referred to by Dr. Medin, only P146S appears in Claim 36 of the '388 Patent. Dr. Medin ignores the explicit teachings of the '319 Patent Publication that would have discouraged a person of skill in the art from treating Fabry patients with a P146S mutation with migalastat. Indeed, the '319 Patent Publication discloses—based on the results of the in vitro activity assay described in the '319 Patent Publication—that Fabry patients with a P146S mutation are non-responsive to migalastat.²¹⁸ For example, the '319 Patent Publication discloses that the P146S mutation is a "[n]on-responsive GLA mutation[]." ²¹⁹ The '319 Patent Publication

²¹⁷ Medin Opening Report, ¶ 145; Ex. C at 3-4, 6-7.

²¹⁸ See, e.g., '319 Patent Publication, at Fig. 18.

²¹⁹ See, e.g., '319 Patent Publication, at Figs. 1A, 18, ¶¶ 0026, 0043, 0177.

also teaches that Fabry patients with a non-responsive α -Gal A mutations should not be treated with migalastat.²²⁰ The '319 Patent Publication states:

In a further embodiment, the invention relates to a method of treating a patient diagnosed with Fabry disease by administering to the patient a therapeutically effective dose of 1-deoxygalactonorigirimycin, or a similar pharmacological chaperone to a patient that expresses a mutation in α -galactosidase A, ***with the proviso that the mutation is not a nonresponsive mutation*** and/or the mutation is not a mutation in which no enzyme is expressed.²²¹

In my opinion, a person of ordinary skill in the art would not be motivated to treat Fabry disease patients with the mutation P146S based on the disclosures of the '319 Patent Publication and would not have a reasonable expectation of success in doing so.

177. Further, Dr. Medin fails to acknowledge that other prior art references suggest treating a Fabry patient who has a non-amenable mutation with migalastat would not be beneficial or even harmful to a patient. Further, it would be unethical for a physician to treat a patient with a drug that the physician knows is not the optimal drug for that patient, and thereby prevent them from receiving the most beneficial treatment for their specific disease. Thus, it is my opinion that Dr. Medin fails to provide any reason why a person of ordinary skill in the art would be motivated to treat such Fabry patients with a reasonable expectation of success upon reading the '319 Patent Publication. Dr. Medin also fails to provide any reason why a person of ordinary skill in the art would be motivated to search for a different answer than the one provided in the '319 Patent Publication on whether a Fabry patient with a P146S mutation would respond to treatment with migalastat.

178. In addition, of the four specific mutations recited in Claim 36 of the '388 Patent, the '319 Patent Publication does not disclose three—namely, G80D, M267T and R356P.

²²⁰ '319 Patent Publication, ¶ 0177.

²²¹ '319 Patent Publication, ¶ 0025 (emphasis added).

Nevertheless, even if a person of ordinary skill in the art were to look for whether any of those three specific mutations had been tested in an in vitro HEK assay, he or she would have found the work of Lukas et al. Lukas et al. tested each of these specific mutations in an in vitro HEK assay and found each to be non-responsive to treatment with migalastat.²²² Thus, in my opinion, a person of ordinary skill in the art would not have been motivated to treat Fabry patients with any of these mutations with migalastat and certainly would not have had a reasonable expectation of success in doing so.

179. Dr. Medin opines that “[t]he specification of the ’388 Patent identifies [the A13P, Q57L, P146S, and I242F] mutations as HEK assay amenable mutations.”²²³ A13P, Q57L, and I242F are not in Claim 36. Regardless, Dr. Medin’s assertion is misleading because the ’319 Patent Publication identifies each of these four mutations as non-responsive.²²⁴ In my opinion, Dr. Medin is using hindsight, and the teachings of the ’388 Patent, for his obviousness analysis with respect to Claim 36 of the ’388 Patent. I understand that the disclosures of the ’388 Patent on these four mutations being amenable should not be used to support the proposition that the invention of the ’388 Patent is obvious when the prior art discloses that these mutations are non-amenable. Dr. Medin further opines that “[a]s being HEK assay amenable is an inherent property of the identified mutations, this claim limitation would have inherently existed in the prior art.”²²⁵ It is not clear to me what Dr. Medin is suggesting. As already discussed, none of

²²² See Jan Lukas et al., *Functional and Clinical Consequences of Novel α -Galactosidase A Mutations in Fabry Disease*, Human Mutation, Vol. 00, No. 0, 1–9 (2015) (ATGAL_00730664); Jan Lukas et al., *Functional Characterisation of Alpha-Galactosidase A Mutations as a Basis for a New Classification System in Fabry Disease*, PLOS Genetics, Vol 9, Issue 8 (Aug. 2013) (ATGAL_09916904 at -910; ATGAL_01136145).

²²³ Medin Opening Report, ¶ 145; Ex. C at 3-4, 6-7.

²²⁴ ’319 Patent Publication, Figs. 1A, 18, ¶¶ 0026, 0043, 0177.

²²⁵ Medin Opening Report, ¶ 145.

the prior art that Dr. Medin relies upon either alone or in combination, teach that a Fabry patient with any of the specific mutations of Claim 36 of the '388 Patent may be amenable to migalastat treatment. To the contrary, the explicit teachings of the '319 Patent Publication that the P146S mutation is “non-responsive” to treatment with migalastat, and other prior art (e.g., Lukas et al.) that disclosed the remaining three mutations in Claim 36 as non-responsive to treatment with migalastat would have taught a skilled person in the art away from using migalastat for treating these patients.

180. Dr. Medin opines that “[a] [person of ordinary skill in the art] would have been motivated to identify patients with GLA mutations suffering from Fabry disease, determine if these mutations are HEK amenable mutations, and once a mutation such as A13P, Q57L, P146S, or I242F, would be determined to be an HEK assay amenable mutation, to administer migalastat to patients having these mutations.”²²⁶ For the reasons explained above, I also disagree with this opinion. For example, with respect to the specific mutations in Claim 36 of the '388 Patent, a person of ordinary skill in the art using the HEK assay described in the '319 Patent Publication would have found P146S to be non-responsive to migalastat and thus would not have been motivated to treat such patients with migalastat with any reasonable expectation of success. Similarly, to the extent a person of ordinary skill in the art was to look for whether one of the other mutations in Claim 36 are responsive or non-responsive, such person of ordinary skill in the art would have found the work of Lukas et al., determined that such mutations were non-responsive to migalastat, and thus would not have been motivated to treat such patients with migalastat with any reasonable expectation of success. Dr. Medin has provided no reason why a person of ordinary skill in the art would have re-tested these mutations, or how the mutation may

²²⁶ Medin Opening Report, ¶ 146 (citing '319 Patent Publication, Fig. 1A); Ex. C at 4.

be re-tested differently, or why they would have had a reasonable expectation of success in treating patients with the mutations in Claim 36 with migalastat. In addition, the '319 Patent Publication discusses a HEK assay that was found to be unreliable in identifying Fabry patients who could benefit from treatment with migalastat. The inability of the assay discussed in the '319 Patent Publication to accurately predict whether a mutation was responsive or non-responsive to migalastat was demonstrated by the failure to reach the primary endpoint in the six-month data for Amicus's phase 3 clinical trial, which used this assay for enrollment.

181. Dr. Medin further opines that the '319 Patent Publication "discloses a method of treating Fabry disease by administering migalastat to a patient."²²⁷ I disagree. The '319 Patent Publication discloses results of an in vitro HEK assay with respect to specific mutations and that some, but not all, mutations are responsive to migalastat. It does not teach a general method of treatment for Fabry disease by administering migalastat to any Fabry patient.

182. Dr. Medin opines that "Lockhart discloses administering the hydrochloride salt of DGJ (i.e., migalastat) to participants at a specific dose level of 150 mg every other day."²²⁸ In my opinion, Dr. Medin overstates the disclosures in Lockhart '093. Lockhart '093 does not disclose that a dose of 150 mg every other day will work for all α -Gal A mutations or even for all amenable mutations. Further, Lockhart '093 does not disclose that 150 mg every other day is an effective dose for Fabry patients with any of the mutations in Claim 36. Dr. Medin relies upon Lockhart '093's discussion of modeling of doses related to isofagomine (IFG), a chaperone considered as a treatment option for Gaucher disease at the time and the disclosure that such

²²⁷ Medin Opening Report, ¶ 146.

²²⁸ Medin Opening Report, ¶ 152 (citing Lockhart '093, ¶¶ 0142, 0151, Exs. 4-6); Ex. C at 6.

model could be applicable to DGJ.²²⁹ This theoretical model does not provide a motivation to treat an actual Fabry patient with a specific dosage of migalastat, especially in light of the many other dose regimens discussed in Lockhart '093, including in Examples 4-6 that Dr. Medin cites.²³⁰

183. Dr. Medin opines that “[a] [person of ordinary skill in the art] would have been aware of the 150 mg every other day dosing of migalastat to treat Fabry Disease and its effectiveness from at least Lockhart '093, and therefore would have been motivated to rely on this teaching to arrive at the 150 mg every other day dosing.”²³¹ Dr. Medin also opines that “[a] [person of ordinary skill in the art] would further have had an expectation of success with this dosing given the teachings of Lockhart '093.”²³² I disagree with these opinions. Lockhart '093 does not disclose that 150 mg every other day is an effective dose for all Fabry patients or for all Fabry patients with an amenable mutation. Nor does Lockhart '093 even suggest that 150 mg every other day is the preferred dose and dose regimen of migalastat hydrochloride for any Fabry patient. Lockhart '093 relies on theoretical dosing models and preliminary data for enrollment of phase 2 studies related to migalastat hydrochloride where a number of different doses and dose regimens were used.²³³ A person of ordinary skill in the art would have understood Lockhart '093 to be a preliminary investigation into dosing of pharmacological chaperones like migalastat hydrochloride and not some definitive reference of the proper dose of migalastat hydrochloride for all Fabry patients, as Dr. Medin suggests.

²²⁹ Lockhart '093, ¶¶ 0142, 0151.

²³⁰ Lockhart '093, ¶¶ 0142, 0151; *see also supra* § VIII.A.5.

²³¹ Medin Opening Report, ¶ 153; Ex. C at 6.

²³² Medin Opening Report, ¶ 153; Ex. C at 6.

²³³ *See* Lockhart '093, Exs. 4-6.

184. Dr. Medin then opines that “claim 7 would have been obvious over the ’319 patent publication and the knowledge of a [person of ordinary skill in the art].”²³⁴ I understand from counsel that Claim 7 is not asserted, and I have been asked to limit my response to Claim 36. Dr. Medin then opines “claim 36 of the ’388 patent would have been obvious over the ’319 patent publication in view of Lockhart and the knowledge of a [person of ordinary skill in the art].”²³⁵ In my opinion, the ’319 Patent Publication in view of Lockhart ’093 and the knowledge of a person or ordinary skill in the art does not render obvious Claim 36. In addition, although Dr. Medin refers to the ’319 Patent Publication in view of Lockhart ’093 in combination with the knowledge of a person of ordinary skill in the art, Dr. Medin does not identify any “knowledge of a [person of ordinary skill in the art]” that he is using as part of the obviousness analysis for Claim 36. In my opinion, Dr. Medin has failed to show Claim 36 is obvious over the ’319 Patent Publication in view of Lockhart ’093 and the knowledge of a person of ordinary skill in the art. For all the reasons discussed herein, in my opinion, Dr. Medin has failed to prove that Claim 36 is obvious. Based on my review of the prior art references and the disclosures cited, in my opinion, Claim 36 is not obvious and there is no motivation to combine the references with any reasonable expectation of success in reaching the invention of Claim 36. Dr. Medin generally fails to acknowledge the fact that the prior art references he relies on do not disclose treating Fabry patients with the specific mutations in Claim 36 and he fails to explain how a person of ordinary skill in the art would reach such a method of treatment for those specific mutations based on the references he relies upon, why a person of ordinary skill in the art would combine them, and why such a person would have a reasonable expectation of success in doing so.

²³⁴ Medin Opening Report, ¶ 146; Ex. C at 3-4.

²³⁵ Medin Opening Report, ¶ 152; Ex. C at 6.

b) Asserted Combination 2: Undisclosed Combination of Wu, Germain 2012, Giugliani, and/or Benjamin 2016 and the Knowledge of a Person of Ordinary Skill in the Art; Asserted Combination 3: Wu and/or Germain 2012 in View of Benjamin 2016 and/or Giugliani and the Knowledge of a Person of Ordinary Skill in the Art

185. With respect to Claim 36, Dr. Medin opines that “by 2011, more than 600 disease-causing mutations in the GLA gene had been identified . . . and by March 2016, more than 800 disease-causing mutations in the GLA gene had been identified”²³⁶ In my opinion, the high number of unique GLA mutations that had been discovered adds to the complexity of the methods of treatment with migalastat and supports the nonobviousness of Claim 36. In my opinion, it would not have been obvious to try treatment with migalastat for Fabry patients with the mutations in Claim 36, especially given the unpredictability of whether or not Fabry patients with a given mutation would respond to treatment with migalastat; further, a person of ordinary skill in the art would not have had a reasonable expectation of success with respect to treating Fabry patients that carry one of the mutations in Claim 36 with migalastat.

186. Dr. Medin opines that “[i]t was well known that migalastat selectively binds and stabilizes α -Gal A, and that a HEK-293 cell-based assay could be used to identify mutant forms of α -Gal A that are responsive to migalastat.”²³⁷ Dr. Medin also opines that “[t]he prior art further teaches use of a HEK-293 cell-based assay to identify patients with α -Gal A mutations that are amenable to migalastat treatment.”²³⁸ In my opinion, Dr. Medin has vastly overstated the state of the field at the time the application leading to the ’388 Patent was filed. In fact, the HEK-293 cell-based assay from the ’319 Patent Publication, Wu, Germain 2012, and Giugliani

²³⁶ Medin Opening Report, ¶ 147.

²³⁷ Medin Opening Report, ¶ 147; Ex. C at 6-7.

²³⁸ Medin Opening Report, ¶ 148; Ex. C at 6-7.

was found to be unable to accurately identify which patients to treat with migalastat. In addition, Benjamin 2016 did not disclose full information about the Migalastat Amenability Assay, including critical information about which mutations were found amenable or not in that assay. Further, Benjamin 2016 does not disclose treatment of Fabry patients with any of the specific mutations in Claim 36. Indeed, pharmacological chaperones were a relatively new avenue of treatment that was being explored. As of the priority date, there were no FDA approved pharmacological chaperones for any disease, let alone for Fabry disease.²³⁹ Although there were theories about how migalastat may be able to selectively bind and stabilize α -Gal A in certain situations, it was unknown when this would occur; and the disclosures in the art at the time suggested that it was highly unpredictable which mutated α -Gal A would be stabilized by migalastat. Further, the HEK assay referred to in those references was determined to be unreliable, including because it was used for enrollment in Amicus's phase 3 clinical studies, which resulted in the 011 study failing to meet its endpoint for the first six months of data.

187. Dr. Medin opines that “it would have been obvious for a [person of ordinary skill in the art] to simply carry out the steps of a known cell and enzyme assay to identify the naturally-occurring α -galactosidase A mutations recited in claim 7.”²⁴⁰ As an initial matter, I

²³⁹ See e.g., Keyzor I., et al., (2023) Therapeutic Role of Pharmacological Chaperones in Lysosomal Storage Disorders: A Review of the Evidence and Informed Approach to Reclassification, *Biomolecules* **13**(8):1227 (“The term “pharmacological chaperone therapy” or “PCT” was first coined in 2000 to describe the category of exogenously administered small molecules that restore folding and trafficking defects of misfolded proteins in LSDs. The EMA approved the first commercially available PCT, migalastat (Galafold®; Amicus Therapeutics Inc., Philadelphia, PA, USA), in 2016, for long-term treatment of adults with Fabry disease who have an amenable mutation (i.e., a mutation that is responsive to treatment).”) (internal citation omitted) (ATGAL_10161626 at -627); May 31, 2016, Amicus Therapeutics Announces European Commission Approval for Galafold™ (Migalastat) in Patients with Fabry Disease in European Union (ATGAL_07336052 at -052); Moran, N., (2018) FDA Approves Galafold, a Triumph for Amicus, *Nat. Biotech.* 36:91 (ATGAL_10161450 at -450).

²⁴⁰ Medin Opening Report, ¶ 148; Ex. C at 3-4.

understand that Claim 7 is not asserted. To the extent Dr. Medin intended to say Claim 36, for all of the reasons discussed above, I disagree. Wu, Germain 2012, and Giugliani would discourage a person of skill in the art from treating Fabry patients with one of the mutations in Claim 36 with migalastat, including because had a person of ordinary skill in the art used the assay discussed in these references to determine whether Fabry patients with the mutations in Claim 36 were responsive to treatment with migalastat, he or she would have found that those mutations are categorized as nonresponsive and therefore would not have been motivated to treat such Fabry patients with migalastat. For example, as discussed above, in my opinion, a person of ordinary skill in the art would not have a reasonable expectation of success in reaching the invention claimed in Claim 36 of the '388 Patent because of the number of different α -Gal A mutations and unpredictability of whether a Fabry patient with any specific α -Gal A mutation can be treated with migalastat. Further, none of the prior art references that Dr. Medin cites report that any of the mutations in Claim 36 can be treated with migalastat; and Dr. Medin points to no reason why a person of ordinary skill in the art would have found these mutations in particular and been motivated to treat patients with one of those mutations, or any reason why a person of ordinary skill in the art would have had a reasonable expectation of success in doing so. As noted above, for each of the mutations in Claim 36, the prior art actually discourages treatment of these Fabry patients with migalastat.²⁴¹ As such, a person of ordinary skill in the art would have had no reason to re-test these mutations, nor would the person of ordinary skill in the art have had any guidance as to how to test these mutations in a different assay based on these

²⁴¹ '319 Patent Publication at Figs. 17 & 18; Jan Lukas et al., *Functional and Clinical Consequences of Novel α -Galactosidase A Mutations in Fabry Disease*, Human Mutation, Vol. 00, No. 0, 1–9 (2015) (ATGAL_00730664); Jan Lukas et al., *Functional Characterisation of Alpha-Galactosidase A Mutations as a Basis for a New Classification System in Fabry Disease*, PLOS Genetics, Vol 9, Issue 8 (Aug. 2013) (ATGAL_09916904 at -910; ATGAL_01136145).

prior art references. Further, Dr. Medin points to no reason why a person of ordinary skill in the art would have found these mutations in particular and been motivated to re-test these mutations to treat patients with one of those mutations, much less how the mutations may be re-tested, or any reason why a person of ordinary skill in the art would have had a reasonable expectation of success in doing so.

188. Dr. Medin opines that “[a] [person of ordinary skill in the art] would have been motivated with a reasonable expectation of success to combine the teachings of Wu, Germain 2012, Benjamin (2016), and/or Giugliani, at least because each is directed to the use of migalastat in the treatment of Fabry disease and/or the evaluation of mutations in the α -galactosidase A gene in patients with Fabry disease that inform treatment options for Fabry disease, including treatment with migalastat.”²⁴² I disagree. In my opinion, a person of ordinary skill in the art would not have combined results or teachings from Benjamin 2016 with those of Wu, Germain 2012, and Giugliani to treat Fabry patients with the specific mutations of Claim 36 of the ’388 Patent because they would have had no reason to do it. More importantly, even if a person of ordinary skill in the art were to combine such references, such person of ordinary skill in the art would not be motivated to reach the invention claimed in Claim 36 with any reasonable expectation of success for all of the reasons described above, including, e.g., because none of the mutations at issue in Claim 36 are disclosed in these references as being amenable to migalastat. Dr. Medin also opines that “a [person of ordinary skill in the art] seeking to improve upon the existing treatments of Fabry disease would have been motivated with a reasonable expectation of success to combine the disclosures of Wu, and/or Germain 2012 in view of Benjamin (2016)

²⁴² Medin Opening Report, ¶ 149.

and/or Giugliani, and the knowledge of a [person of ordinary skill in the art].”²⁴³ He also opines that “a [person of ordinary skill in the art] would have been motivated to combine the teachings of Wu, Germain 2012, Giugliani, and/or Benjamin (2016) because they all have complementary teachings and show consistent outcomes” and “[t]herefore, a [person of ordinary skill in the art] would also have at least a reasonable expectation of success in doing so and arriving at the claimed invention.”²⁴⁴ I also disagree with these opinions. Dr. Medin fails to explain why a person of ordinary skill in the art would be seeking to improve upon existing treatments. He also fails to explain exactly which disclosures of Wu, Germain 2012, Benjamin 2016, and Giugliani a person of ordinary skill in the art would combine and why there is a motivation to combine, and why doing so would result in a reasonable expectation of success. Simply saying they have “complementary teachings and show consistent outcomes” does nothing to explain why there would be a reasonable expectation of success. Further, although Dr. Medin mentions knowledge of a person of ordinary skill in the art, he fails to identify what exactly that knowledge is.

189. Dr. Medin opines that “Wu discloses the administration of ‘a dose of 150 mg [migalastat hydrochloride] every other day’ as a potential treatment for Fabry disease.”²⁴⁵ Dr. Medin further opines that Wu “discloses ‘the administration of different [migalastat hydrochloride] doses (50, 150, or 250 mg) and with various regimens.’”²⁴⁶ Dr. Medin also opines that “Wu discloses that ‘most mutant forms [of α -Gal A] that were tested at both lower and higher doses showed a ‘good’ response at either dose. This suggests that a single common dose and regimen of AT1001 may be sufficient to mediate a response of the enzyme in vivo for

²⁴³ Medin Opening Report, ¶ 149.

²⁴⁴ Medin Opening Report, ¶ 150.

²⁴⁵ Medin Opening Report, ¶ 154 (citing Wu at 974); Ex. C at 4, 6.

²⁴⁶ Medin Opening Report, ¶ 154 (citing Wu at 975); Ex. C at 4, 6.

many mutant forms of α -Gal A.”²⁴⁷ Dr. Medin overstates what Wu discloses. Wu actually discloses that:

The degree of consistency found in the current comparison of HEK-293 cell-based and in vivo mutant α -GAL A responses does not necessarily indicate the degree of consistency that would be seen with any particular dose or regimen of [migalastat hydrochloride]. This is because the in vivo α -GAL A responses analyzed here were obtained following different [migalastat hydrochloride] doses (50, 150, or 250 mg) and with various regimens (every other day, twice per day, or every day), according to the different clinical study protocols.²⁴⁸

In my opinion, this is a disclosure of specific doses and dose regimens provided to a limited number of specific Fabry patients with specific mutations. It does not disclose that any such dosages or regimens could be used to treat Fabry patients with other α -Gal A mutations or that a specific dose or regimen is recommended for Fabry patients with the mutations in Claim 36.

190. Dr. Medin opines that Germain 2012 discloses “oral administration of 150 mg migalastat HCl every other day.”²⁴⁹ Dr. Medin again overstates this disclosure because like Wu, Germain 2012 relates to treatment of a limited number of specific Fabry patients with specific Fabry mutations at specific doses and dose regimens. It does not disclose that a specific dose or regimen is recommended for Fabry patients with the mutations in Claim 36.

191. Dr. Medin opines that Giugliani discloses “the evaluation of ‘the safety and pharmacodynamics of migalastat hydrochloride, an investigational pharmaceutical chaperone given orally every other day (QOD) to females with FD” and “the oral administration of migalastat hydrochloride at doses of 50 mg, 150 mg, and 250 mg every other day (QOD) to females with Fabry disease.”²⁵⁰ Dr. Medin again overstates this disclosure because like Wu and

²⁴⁷ Medin Opening Report, ¶ 154 (citing Wu at 975); Ex. C at 4, 6.

²⁴⁸ Wu at 975.

²⁴⁹ Medin Opening Report, ¶ 155 (citing Germain 2012 at Abstract); Ex. C at 4, 6.

²⁵⁰ Medin Opening Report, ¶ 155 (citing Giugliani at Abstract); Ex. C at 4, 6.

Germain 2012, Giugliani relates to treatment of a limited number of specific Fabry patients with specific Fabry mutations at specific doses and dose regimens. It does not disclose that a specific dose or regimen is recommended for Fabry patients with the mutations in Claim 36

192. Dr. Medin opines that Benjamin 2016 discloses “administration of 150 mg migalastat HCl.”²⁵¹ Dr. Medin’s reliance on Benjamin 2016 is also misplaced because Benjamin 2016 does not disclose treatment of Fabry patients with the G80D, P146S, M267T, or R356P mutations in Claim 36 of the ’388 Patent, nor does it disclose use of 150 mg every other day with respect to those mutations. In fact, Benjamin 2016 does not identify any amenable mutation based on the Migalastat Amenability Assay.

193. Dr. Medin opines that “a [person of ordinary skill in the art] would have been motivated to combine the teachings of Wu, Germain 2012, Giugliani, and/or Benjamin (2016) for this dosing because they all have complementary teachings and show consistent outcomes, therefore, a [person of ordinary skill in the art] would also have an expectation of success in doing so.”²⁵² I disagree. Dr. Medin fails to explain exactly which disclosures of Wu, Germain 2012, Benjamin 2016, and Giugliani a person of ordinary skill in the art would combine and why there is a motivation to combine, and why doing so would result in a reasonable expectation of success. Simply saying they have “complementary teachings and show consistent outcomes” does nothing to explain why there would be a reasonable expectation of success. Further, although Dr. Medin mentions the knowledge of a person of ordinary skill in the art, he fails to identify what that knowledge is.

²⁵¹ Medin Opening Report, ¶ 155 (citing Benjamin 2016 at 4); Ex. C at 6.

²⁵² Medin Opening Report, ¶ 156.

194. It is unclear what combination(s) Dr. Medin is relying upon for his analysis of Claim 36. Because Dr. Medin's obviousness combinations are unclear, I reserve the right to supplement my opinions based on any additional and/or clarifying opinions that Dr. Medin renders with respect to Claim 36. Further, Dr. Medin fails to identify what he is using as his base reference, how he is modifying it and what reference he is modifying it with, and why a person of ordinary skill in the art would be motivated to modify the reference or have had a reasonable expectation of success in such a combination. Dr. Medin more generally fails to explain how he is combining the prior art references and how and why, in his opinion, such references would cause a person of ordinary skill in the art to reach the claimed invention. In addition, he generally fails to acknowledge the fact that the prior art references he relies on do not disclose treating Fabry patients with the specific mutations in Claim 36 and even teach away from the invention. Further, he fails to explain how a person of ordinary skill in the art would reach such a method of treatment for those specific mutations based on the references he relies upon.

195. Dr. Medin opines that "claim 36 would have been obvious over Wu and/or Germain 2012 in view of Benjamin (2016), and/or Giugliani, and the knowledge of a [person of ordinary skill in the art]." ²⁵³ For all the reasons discussed herein, in my opinion, Dr. Medin has failed to prove that Claim 36 is obvious. Based on my review of the prior art references and the disclosures cited, in my opinion, Claim 36 is not obvious and there is no motivation to combine the references with any reasonable expectation of success in reaching the invention of Claim 36. Dr. Medin generally fails to acknowledge the fact that the prior art references he relies on do not disclose treating Fabry patients with the specific mutations in Claim 36 and he fails to explain how a person of ordinary skill in the art would reach such a method of treatment for those

²⁵³ Medin Opening Report, ¶ 157; Ex. C at 6.

specific mutations based on the references he relies upon, why a person of ordinary skill would combine them, and why such a person would have a reasonable expectation of success in doing so.

D. Claims 17 and 23 of the '489 Patent

196. As an initial matter, it is unclear to me what combination of references Dr. Medin is using for his prior art combinations for Claims 17 and 23 of the '489 Patent. Dr. Medin opines in the summary of his opinions that:

[b]y way of example, the asserted claims are rendered obvious by the following combinations:

- 1) The '319 patent publication in view of Lockhart 093 and the knowledge of a [person of ordinary skill in the art]
- 2) Wu, Germain [2012], Benjamin [2016], and/or Giugliani and the knowledge of a [person of ordinary skill in the art]
- 3) Wu and/or Germain [2012] in view of Benjamin [2016] and/or Giugliani and the knowledge of a [person of ordinary skill in the art.]²⁵⁴

Dr. Medin seems to imply that there could be additional combinations, but he does not explicitly disclose what those additional combinations might be. Accordingly, I will respond to the opinions and specific combinations that Dr. Medin actually analyzed in his report, and I reserve the right to respond to any additional combinations should Dr. Medin later render an opinion as to such combinations.

197. Moreover, this list results in dozens of possible combinations of the prior art references. Dr. Medin does not actually analyze each of these combinations in his report. Thus, it is unclear what teaching(s) Dr. Medin proposes to take from each reference and why a person of ordinary skill in the art would have been motivated to combine those elements or teachings

²⁵⁴ Medin Opening Report, ¶ 13; Ex. C at 9-10, 12-13.

with a reasonable expectation of success. Instead, Dr. Medin's only obviousness analysis is him analyzing six references, the '319 Patent Publication, Lockhart '093, Wu, Germain 2012, Benjamin 2016, and Giugliani individually without specifying how to combine them within the context of his proposed obviousness combinations let alone why a person of ordinary skill in the art would be motivated to combine those references in such a way. For example, Dr. Medin fails to explain what reference he is starting with and how he is modifying such reference with the other prior art references.²⁵⁵ Accordingly, I will respond to the opinions and combinations that Dr. Medin actually included in his report regarding the disclosed combinations, and I reserve the right to respond to any additional opinions about those combinations or combinations should Dr. Medin later render any opinion about what and how the specific references are to be combined and/or the motivation to combine or modify such specific references.

1. Claim 17

198. Claim 17 of the '489 Patent depends from Claim 11. The claim language is:

11. A method of treating Fabry disease, the method comprising administering migalastat to a patient in need thereof, wherein the patient has an α -galactosidase A protein comprising a HEK assay amenable mutation selected from the group consisting of A13T, N34T, M42K, L54F, P60T, E87D, L89F, Y123C, H125L, I133M, K140T, F145S, P146R, Y152H, D165G, p.M187_S188dup, V199G, M208R, I219L, N224T, Q250R, G261C, G271D, M284V, I303F, D322N, G325R, K326N, G334E, E358Q, E358D, G361E, G375E, T412N and M421V.

17. The method of claim 11, wherein the patient is administered about 150 mg of migalastat hydrochloride every other day.

²⁵⁵ See generally Medin Opening Report, § IX.C (element by element analysis of the asserted claims of the '489 patent); see also Medin Opening Report, Exhibit C (claim chart including list of citations to each of the six asserted prior art references without separating by combination).

199. Based on my review of Dr. Medin’s report, it is unclear what combinations Dr. Medin asserts for Claim 17. Dr. Medin lists only the following combinations in the summary of his opinions:

- 1) The ’319 patent publication in view of Lockhart ’093 and the knowledge of a person of ordinary skill in the art;
- 2) Wu, Germain [2012], Benjamin 2016, and/or Giugliani and the knowledge of a person of ordinary skill in the art;
- 3) Wu and/or Germain [2012] in view of Benjamin 2016 and/or Giugliani and the knowledge of a person of ordinary skill in the art.²⁵⁶

200. Regarding the first combination—the ’319 Patent Publication in view of Lockhart ’093 and the knowledge of a person of ordinary skill in the art—Dr. Medin did not identify what knowledge a person of ordinary skill in the art would have had that is relevant to this combination or why a person of ordinary skill in the art would have been motivated to use that knowledge to modify what is disclosed in the ’319 Patent Publication in view of Lockhart ’093.

201. Regarding the second combination—Wu, Germain 2012, Benjamin 2016, and/or Giugliani, and the knowledge of a person of ordinary skill in the art—it is unclear exactly which of those references he is combining and how those references are being combined. Dr. Medin discusses each of the four references individually before alleging in a conclusory fashion that they could be combined with no explanation of how they would be combined.²⁵⁷ Dr. Medin

²⁵⁶ Medin Opening Report, ¶ 13; Ex. C at 8-9.

²⁵⁷ See Medin Opening Report, ¶ 178 (“In addition, a POSA [person of ordinary skill in the art] would have been motivated to combine the teachings of Wu, Germain [2012], Giugliani and/or Benjamin (2016) because they all have complementary teachings and show consistent outcomes, therefore, a POSA [person of ordinary skill in the art] would also have an expectation of success in doing so.”); see also Medin Opening Report, ¶ 172 (“A POSA [person of ordinary skill in the art] would have been motivated with a reasonable expectation of success to combine the teachings of Wu, Germain 2012, Benjamin (2016), and/or Giugliani, at least because each is directed to the use of migalastat in the treatment of Fabry disease and/or the evaluation of

again failed to identify what knowledge a person of ordinary skill in the art would have had that is relevant to this combination or why a person of ordinary skill in the art would have been motivated to use that knowledge to modify what is disclosed in the references cited by Dr. Medin.

202. Regarding the third combination—Wu and/or Germain 2012 in view of Benjamin 2016 and/or Giugliani and the knowledge of a person of ordinary skill in the art—it is unclear exactly which of those references he is combining and how those references are being combined. Like with the second combination, Dr. Medin discusses each of the four references individually before alleging in a conclusory fashion that they would be combined, with no explanation of how they would be combined or why a person of ordinary skill in the art would combine them.²⁵⁸ Again, Dr. Medin failed to identify what knowledge a person of ordinary skill in the art would have had that is relevant to this combination or why a person of ordinary skill in the art would have been motivated to use that knowledge to modify what is disclosed in the references cited by Dr. Medin.

203. In my opinion, as discussed further below, Dr. Medin’s combinations do not disclose the limitations of Claim 17 and do not render Claim 17 obvious.

a) Asserted Combination 1: the ’319 Patent Publication in view of Lockhart ’093 and the Knowledge of a Person of Ordinary Skill in the Art

mutations in the α -galactosidase A gene in patients with Fabry disease that inform treatment options for Fabry disease, including treatment with migalastat.”).

²⁵⁸ See Medin Opening Report, ¶ 172 (“Furthermore, a POSA [person of ordinary skill in the art] seeking to improve upon the existing treatments of Fabry disease would have been motivated with a reasonable expectation of success to combine the disclosures of Wu, and/or Germain 2012 in view of Benjamin (2016) and/or Giugliani, and the knowledge of a POSA [person of ordinary skill in the art].”).

204. To support his obviousness analysis, Dr. Medin cites to Proposed Claim 10 of the '319 Patent Publication to argue that methods for treating Fabry with migalastat was known.²⁵⁹ Dr. Medin also opines that the '319 Patent Publication “discloses a method of treating Fabry disease by administering migalastat to a patient.”²⁶⁰ I disagree. The '319 Patent Publication discloses results of an in vitro HEK assay with respect to specific mutations and that some, but not all, mutations are responsive to migalastat. It does not teach a general method of treatment for Fabry disease by administering migalastat to any Fabry patient.

205. Dr. Medin relies on Proposed Claim 10 of the '319 Patent Publication, which states:

10. A method of treating a patient diagnosed with Fabry disease which comprises administering to the patient a therapeutically effective dose of 1-deoxygalactonorjirimycin, wherein the patient expresses a mutant α -galactosidase A selected from the group consisting of the α -galactosidase A mutations A257D, A257G, A257P, A291T, A292T, A307T, **A309P**, **A352V**, A368T, A73V, A97V, C174G, C174R, C56F, C56Y, D165H, D313G, D322E, D55V, E203V, F169S, G171R, G183A, G183V, G258R, G258V, G261D, G325S, G360D, G360S, G85D, G85M, I117S, I198T, I239T, I253T, I289S, I319T, I359T, K185E, K308N, L166G, L16H, L19P, L243W, L36F, L36S, L372P, L403S, L54P, M290I, M290L, M296L, M296T, M42L, M42R, M76T, M96I, N53L, P205S, P293T, P409A, P409T, P60L, Q107L, Q250P, Q312R, Q321H, Q321L, R301G, **R356G**, S238N, S247C, T282A, T410I, V339E, W162G, W349S, Y152C, Y184C, Y200C, Y207H and Y216C.²⁶¹

From this list of over eighty mutations, Dr. Medin then focuses on only a few cherry-picked mutations based on their amino acid positions, namely A309P, A352V, and R356G (bolded and underlined above).²⁶² None of the mutations in Claim 17 are at any of these three amino acid positions.

²⁵⁹ Medin Opening Report, ¶ 159; Ex. C at 8.

²⁶⁰ Medin Opening Report, ¶ 164; Ex. C at 8.

²⁶¹ '319 Patent Publication, Proposed Claim 10.

²⁶² Medin Opening Report, ¶ 159 (calling attention to A309P, A352V, and R356G).

206. Similarly, Dr. Medin also opines that the '319 Patent Publication “discloses that the mutations A20P, I242N, A309P, A352V, R356G, and R356W are responsive to migalastat, i.e., they are HEK assay amenable mutations.”²⁶³ Dr. Medin then opines that “a [person of ordinary skill in the art] would know that amino acid positions 20, 242, 309, 352, and 356 in α -galactosidase A have missense mutations in Fabry patients and would therefore be motivated to explore other mutations at the same amino acid positions.”²⁶⁴

207. As a preliminary matter, Dr. Medin seems to be mixing up the concepts of responsiveness in the HEK assay described in the '319 Patent Publication with the concept of HEK assay amenable mutations described in the '489 Patent. In drawing this inappropriate parallel, Dr. Medin is using the '489 Patent's disclosures and thus is using hindsight to support his obviousness arguments. The assay in the '319 Patent Publication is different than the assay in the '489 Patent, and Claim 17 refers to a “HEK assay amenable mutation” in the Migalastat Amenability Assay—the assay described in the '489 Patent, not the assay described in the '319 Patent Publication.

208. Further, I disagree with Dr. Medin's opinions for several other reasons. *First*, as described above in the technology background (§VI), Fabry disease is difficult to diagnose and treat because there are many different α -Gal A mutations that cause Fabry disease. Each mutation may cause different symptoms, ultimately causing different presentations of the disease in each patient. A disclosure that a patient with one of the α -Gal A mutations, for example, as in Proposed Claim 10 of the '319 Patent Publication, could be treated with migalastat does not inform a person of ordinary skill in the art whether other Fabry disease patients with different α -

²⁶³ Medin Opening Report, ¶ 162.

²⁶⁴ Medin Opening Report, ¶ 162.

Gal A mutations could be treated with migalastat. Further, the '319 Patent Publication discloses examples of an α -Gal A mutation at a specific amino acid location being responsive to treatment with migalastat and a different mutation at the same location is not.²⁶⁵ In fact, the '319 Patent Publication itself recognizes that there is no way to predict whether a Fabry patient with a specific mutation will be responsive or not to treatment with migalastat prior to testing.²⁶⁶ This remains true even if the mutation occurs at the same position in the α -Gal A protein. For example, the '319 Patent Publication discloses that the L16H, N34K, R112H, N224S, A352V mutations are responsive to treatment with migalastat but the L16P, N34S, R112C, R112S, N224D, A352P, A352D mutations are non-responsive to treatment with migalastat.²⁶⁷ Thus, a person of ordinary skill in the art would not be motivated based on the disclosures of the '319 Patent Publication to look for other α -Gal A mutations at the same amino acid position as a mutation that is reported as responsive to treatment with migalastat in the '319 Patent Publication. The '319 Patent Publication, including Proposed Claim 10, does not include any of the α -Gal A mutations in Claim 17 of the '489 Patent and therefore does not disclose or render obvious treatment of Fabry patients with the specific α -Gal A mutations of Claim 17 with migalastat. Just because a specific mutation at a particular amino acid position results in an α -Gal A protein that is responsive to treatment with migalastat as measured by the HEK assay

²⁶⁵ '319 Patent Publication, at Fig. 17 (showing responsive GLA mutations L16H, N34K, R112H, N224S, A352V); '319 Patent Publication, Fig. 18 (showing non-responsive GLA mutations L16P, N34S, R112C, R112S, N224D, A352P, A352D).

²⁶⁶ See, e.g., '319 Patent Publication, ¶ 0150 ("DGJ-responsive and non-responsive mutant forms did not appear to be located to particular regions or domains on the α -Gal A protein structure."); '319 Patent Publication, ¶ 0146 ("No significant correlation between response and location on the protein sequence of a mutation was observed, suggesting that responsive as well as non-responsive mutations are distributed widely across the entire protein.").

²⁶⁷ See '319 Patent Publication, at Figs. 17 & 18.

discussed in the '319 Patent Publication does not allow a person of ordinary skill in the art to predict which other mutations at the same amino acid position may be responsive.

209. **Second**, none of the A20P, I242N, A309P, A352V, R356G, and R356W mutations, to which Dr. Medin specifically pointed, are recited in Claim 17 of the '489 Patent. Dr. Medin does not explain how the disclosure of these specific mutations of the '319 Patent Publication could have led a person of ordinary skill in the art to treat Fabry patients with one of the specific mutations in Claim 17 with migalastat. And further, none of the mutations in Claim 17 of the '489 Patent are at amino acid positions 20, 242, 309, 352, or 356.

210. **Third**, the '319 Patent Publication discloses that some α -Gal A mutations are responsive to treatment with migalastat and some are not.²⁶⁸ In addition, the '319 Patent Publication references hundreds of missense mutations and there are many different positions for possible mutations. Dr. Medin cherry picks these amino acid positions for a select few of the hundreds of mutations based on hindsight. Dr. Medin presents no reason why a person of ordinary skill in the art would look to these few mutations rather than the hundreds of others in the '319 Patent Publication.

211. Further, Dr. Medin also opines that “the specification of the '489 Patent identifies [A20P, I242N, A309P, A352V, R356G, and R356W] mutations as HEK assay amenable.”²⁶⁹ . But, whether these mutations are disclosed as amenable or not in the '489 Patent is not relevant because none of these mutations are in Claim 17 of the '489 Patent.

212. Dr. Medin further opines that “[a]s being HEK assay amenable is an inherent property of the identified mutations, this claim limitation would have inherently existed in the

²⁶⁸ See, e.g., '319 Patent Publication, at Fig. 17 & 18.

²⁶⁹ Medin Opening Report, ¶ 163.

prior art.”²⁷⁰ It is not clear to me what Dr. Medin is suggesting and Dr. Medin ignores that none of the mutations he points to are in Claim 17 and none of the mutations in Claim 17 are in the ’319 Patent Publication.

213. Dr. Medin opines that “[a] [person of ordinary skill in the art] would have been motivated to identify patients with GLA mutations suffering from Fabry disease, determine if these mutations are HEK amenable mutations, and once a mutation such as A13P, Q57L, P146S, or I242F, would be determined to be an HEK assay amenable mutation, to administer migalastat to patients having these mutations.”²⁷¹ For the reasons explained above for Claim 8 of the ’388 Patent, I also disagree with this opinion. Further, this argument is especially inapplicable to Claim 17 of the ’489 Patent because none of A13P, Q57L, P146S or I242F are in Claim 17 of the ’489 Patent. In addition, ’319 Patent Publication reports these four mutations as non-responsive to migalastat and a person of ordinary skill in the art would not be motivated to treat such patients with migalastat with any reasonable expectation of success. In addition, the ’319 Patent Publication discusses a HEK assay that was found to be unreliable in identifying Fabry patients who could benefit from treatment with migalastat. The inability of the assay discussed in the ’319 Patent Publication to accurately predict whether a mutation was responsive or non-responsive to migalastat was demonstrated by the failure to reach the primary endpoint in the six-month data for Amicus’s phase 3 clinical trial, which used this assay for enrollment.

214. Dr. Medin then opines that “[c]laim 11 would have been obvious over the ’319 patent publication and the knowledge of a [person of ordinary skill in the art].”²⁷² As an initial

²⁷⁰ Medin Opening Report, ¶ 163.

²⁷¹ Medin Opening Report, ¶ 164.

²⁷² Medin Opening Report, ¶ 164; Ex. C at 8.

matter, Dr. Medin did not identify this alleged combination in the summary of his opinions (Medin Opening Report, ¶ 13), and it is unclear if Dr. Medin is asserting this as a standalone combination. Further, I understand from counsel that Claim 11 is not asserted, and I have been asked to respond only as to Claim 17. To the extent Dr. Medin intended to refer to Claim 17, I disagree with his opinions.

215. With respect to the additional limitations of Claim 17, Dr. Medin opines that “Lockhart discloses administering the hydrochloride salt of DGJ (i.e., migalastat) to participants at a specific dose level of 150 mg every other day.”²⁷³ In my opinion, Dr. Medin overstates the disclosures in Lockhart ’093. Lockhart ’093 does not disclose that a dose of 150 mg every other day will work for all α -Gal A mutations or even for all amenable mutations. Further, Lockhart ’093 does not disclose that 150 mg every other day is an effective dose for Fabry patients with any of the mutations in Claim 17. Dr. Medin relies upon Lockhart ’093’s discussion of modeling of doses related to IFG and the disclosure that such model could be applicable to DGJ.²⁷⁴ This theoretical model does not provide a motivation to treat a Fabry patient with a specific dosage, especially in light of the many other dose regimens discussed in Lockhart ’093, including in the Examples 4-6 that Dr. Medin cites.²⁷⁵

216. Dr. Medin opines that “[a] [person of ordinary skill in the art] would have been aware of the 150 mg every other day dosing of migalastat to treat Fabry Disease and its effectiveness from at least Lockhart ’093, and therefore would have been motivated to rely on this teaching to arrive at the 150 mg every other day dosing.” Dr. Medin also opines that “[a]

²⁷³ Medin Opening Report, ¶ 175 (citing Lockhart ’093 ¶ 0151, Exs. 4-6).; Ex. C at 9.

²⁷⁴ Lockhart ’093, ¶¶ 0142, 0151.

²⁷⁵ Lockhart ’093, ¶¶ 0142, 0151; *see also supra* § VIII.A.5.

[person of ordinary skill in the art] would further have had an expectation of success with this dosing given the teachings of Lockhart '093.”²⁷⁶ I disagree with these opinions. Lockhart '093 does not disclose that 150 mg every other day is an effective dose for all Fabry patients or for all Fabry patients with an amenable mutation. Nor does Lockhart '093 suggest that 150 mg every other day is the preferred dose and dose regimen of migalastat hydrochloride for any Fabry patient. Lockhart '093 relies on theoretical dosing models and preliminary data for enrollment of phase 2 studies related to migalastat hydrochloride where a number of different doses and dose regimens were used.²⁷⁷ A person of ordinary skill in the art would have understood Lockhart '093 to be a preliminary investigation into dosing of pharmacological chaperones like migalastat hydrochloride and not some definitive reference of the proper dose of migalastat hydrochloride for all Fabry patients, as Dr. Medin suggests.

217. Dr. Medin then opines that “claim 17 of the '489 patent would have been obvious over the '319 patent publication in view of Lockhart and the knowledge of a [person of ordinary skill in the art].”²⁷⁸ I disagree. In my opinion, the disclosures of the '319 Patent Publication in view of Lockhart '093 and the knowledge of a person of ordinary skill in the art do not render obvious Claim 17. Further, although Dr. Medin refers to the '319 Patent Publication in view of Lockhart'093 and the knowledge of a person of ordinary skill in the art, Dr. Medin does not identify any “knowledge of a [person of ordinary skill in the art]” that he is using as part of the obviousness analysis in this claim. Thus, in my opinion, Dr. Medin has failed to show that Claim 17 of the '489 Patent is obvious over the '319 Patent Publication in in view of Lockhart

²⁷⁶ Medin Opening Report, ¶ 176; Ex. C at 9-10.

²⁷⁷ See Lockhart '093, Exs. 4-6.

²⁷⁸ Medin Opening Report, ¶ 175; Ex. C at 9-10.

'093 and the knowledge of a person of ordinary skill in the art. Dr. Medin generally fails to acknowledge the fact that the prior art references he relies on do not disclose treating Fabry patients with the specific mutations in Claim 17 and he fails to explain how a person of ordinary skill in the art would reach such a method of treatment for those specific mutations based on the references he relies upon, why a person of ordinary skill in the art would combine them, and why such a person would have a reasonable expectation of success in doing so.

b) Asserted Combination 2: Wu, Germain 2012, Giugliani, and/or Benjamin 2016 and the Knowledge of a Person of Ordinary Skill in the Art;

and

Asserted Combination 3: Wu and/or Germain 2012 in View of Benjamin 2016 and/or Giugliani and the Knowledge of a Person of Ordinary Skill in the Art

218. With respect to the vague combinations of Wu, Germain 2012, Giugliani and/or Benjamin 2016 in view of the knowledge of a person of ordinary skill in the art, and Wu and/or Germain 2012 in view of Benjamin 2016 and/or Giugliani and the knowledge of a person of ordinary skill in the art, Dr. Medin cherry picks what each reference discloses about migalastat and its administration. Dr. Medin, however, does not discuss how these specific disclosures render Claim 17 obvious. For example, according to Dr. Medin, Wu discloses that “migalastat hydrochloride (AT1001, GR181413A) migalastat [is] currently in clinical development to evaluate its safety and efficacy as a potential treatment for Fabry disease” and that “AT1001 (migalastat hydrochloride, 1-deoxygalactonojirimycin) is a pharmacological chaperone for α -Gal A that is in Phase 3 clinical development as a potential therapy for Fabry disease.”²⁷⁹ If Dr. Medin is arguing that these disclosures render Claim 17 obvious, I disagree. Dr. Medin

²⁷⁹ Medin Opening Report, ¶ 160 (quoting Wu at 965, 974); Ex. C at 8, 9.

overreads Wu. Wu's teachings are directed to a certain subset of Fabry patients rather than all Fabry patients, and certainly not all Fabry patients with amenable mutations. For example, Wu states that "a pharmacological chaperone may be a viable treatment for Fabry disease, serving as an alternative to enzyme replacement therapy *for some patients*."²⁸⁰ Wu also recognizes that not all Fabry patients benefit from treatment with migalastat.²⁸¹ Wu also discloses that "[f]urther evaluation of the utility of the HEK-293 cell-based assay for Fabry patient selection for treatment with AT1001 [migalastat hydrochloride] is ongoing."²⁸² In my opinion, a person of ordinary skill in the art would understand this disclosure to mean that Wu is limited to specific Fabry patients in certain of Amicus's phase 2 clinical trials.²⁸³ In addition, although Wu mentions Phase 3 clinical trials, it does not disclose what mutations are being studied in those trials, or whether any such mutations can be treated with migalastat. Further, a skilled artisan would have understood that the initial data from those phase 3 clinical studies was reported by Amicus as "not meet[ing] statistical significance."²⁸⁴ As such, Wu does not provide reliable methods of treating Fabry patients, even for the mutations explicitly discussed in the reference, and the disclosures cannot be used to extrapolate any methods of treatment for Fabry patients who are not discussed in the reference. And Wu does not disclose any method of treating Fabry patients with the mutations in Claim 17 of the '489 Patent. Thus, it is my opinion that Wu does

²⁸⁰ Wu at 965 (emphasis added).

²⁸¹ Wu at 975.

²⁸² Wu at 976.

²⁸³ Wu at Table 2 (discussing FAB-CL-201, FAB-CL-202, and FAB-CL-203 trial data).

²⁸⁴ Amicus Website, Press Release dated Feb. 15, 2013, available at <https://ir.amicusrx.com/news-releases/news-release-details/amicus-therapeutics-presents-additional-6-month-results-phase-3>.

not provide any teaching on how to treat Fabry patients with the α -Gal A mutations from Claim 17 of the '489 Patent.

219. Next, Dr. Medin quotes Germain 2012's disclosure that "[m]igalastat HCl is a candidate pharmacological chaperone that provides a novel genotype-specific treatment for [Fabry disease]."²⁸⁵ Again, Dr. Medin does not discuss how this specific disclosure renders Claim 17 of the '489 Patent obvious. Notwithstanding this deficiency, this disclosure Dr. Medin relies on recognizes that the treatment would be "genotype-specific" and thus cannot be applied to all Fabry patients. In particular, Germain 2012 discloses results from only a limited number of Fabry patients with specific mutations, none of which overlap with those in Claim 17 of the '489 Patent.²⁸⁶ As such, a person of ordinary skill in the art would understand that certain patients would not benefit from treatment with migalastat hydrochloride. Absent specific disclosure that a patient with a specific mutation would benefit from migalastat treatment, a skilled artisan would not be motivated to treat such patients with migalastat. Thus, it is my opinion that Germain 2012 does not provide any teaching on how to treat Fabry patients with one of the mutations in Claim 17 of the '489 Patent.

220. Dr. Medin quotes Giuliani's disclosure of the "evaluation of 'the safety and pharmacodynamics of migalastat hydrochloride, an investigational pharmacological chaperone given orally every other day (QOD) to females with FD.'"²⁸⁷ Again, Dr. Medin does not discuss how this specific disclosure renders Claim 17 of the '489 Patent obvious. Giuliani discloses

²⁸⁵ Medin Opening Report, ¶ 160 (quoting Germain 2012, Abstract); Ex. C at 8-10.

²⁸⁶ See Germain 2012 at Abstract (describing results from two phase 2 studies of nine males with Fabry disease).

²⁸⁷ Medin Opening Report, ¶ 160 (quoting Giuliani, Abstract); Ex. C at 8-10.

specific results related to “nine females with [Fabry disease].”²⁸⁸ As such, a person of ordinary skill in the art would not understand such disclosure could be extrapolated to all Fabry disease patients, regardless of their specific α -Gal A mutation. And Giugliani does not disclose any method of treating Fabry patients with the mutations in Claim 17 of the ’489 Patent. Thus, it is my opinion that Giugliani does not provide any teaching on how to treat Fabry patients with the α -Gal A mutations from Claim 17 of the ’489 Patent.

221. Lastly, Dr. Medin states that Benjamin 2016 “discloses the administration of migalastat HCl to treat Fabry Disease patients.”²⁸⁹ Again, Dr. Medin does not discuss how this specific disclosure renders Claim 17 of the ’489 Patent obvious. Benjamin 2016 does not have any information for any specific α -Gal A mutations or which mutations may be amenable to treatment with migalastat. Without this information, a person of ordinary skill in the art would not be motivated to treat Fabry patients broadly with migalastat. This is especially the case because Benjamin 2016 confirms that migalastat cannot be used for all Fabry patients, and thus mutation specific treatment is required.²⁹⁰ Thus, it is my opinion that Benjamin 2016 does not provide any teaching on how to treat Fabry patients with the α -Gal A mutations from Claim 17 of the ’489 Patent.

222. Dr. Medin opines that “it was well known that a HEK-293 cell-based assay could be used to identify mutant forms of α -Gal A that are responsive to migalastat” and points to disclosures in Germain 2012, Wu, Benjamin, and Giugliani.²⁹¹ In my opinion, this is not an

²⁸⁸ Giugliani, Abstract.

²⁸⁹ Medin Opening Report, ¶ 160 (citing Benjamin 2016 at 1); Ex. C at 8-10.

²⁹⁰ See Benjamin 2016, at 2 (“Approximately 30-50% of patients with FD are estimated to have amenable mutations”).

²⁹¹ Medin Opening Report, ¶¶ 165-166; Ex. C at 8-10.

accurate description of the state of the field at the time of the invention of Claim 17 of the '489 Patent, including for the same reasons discussed above with respect to Claim 8 of the '388 Patent. Wu, Germain 2012, and Giugliani disclose a research-based HEK assay. Benjamin 2016 on the other hand discusses the development of another HEK assay. Dr. Medin is conflating these two distinct assays in his analysis. The HEK-293 cell-based assay used in Germain 2012, Wu, and Giugliani could not accurately predict whether a mutation was responsive or non-responsive to migalastat and the disclosures in Benjamin 2016 do not identify to a person of ordinary skill in the art which mutations are being discussed with respect to the Migalastat Amenability Assay.²⁹² The inability of the assay discussed in Germain 2012, Wu, and Giugliani to accurately predict whether a mutation was responsive or non-responsive to migalastat was demonstrated by the failure to reach the primary endpoint in the six-month data for Amicus's phase 3 clinical trial, which used this assay for enrollment.

223. Dr. Medin cites Giugliani's disclosure that "[p]atients with amenable mutations seemed to demonstrate greater pharmacodynamic response to migalastat HCl compared to patients with non-amenable mutations."²⁹³ Dr. Medin is taking this disclosure out of context. Giugliani's disclosure relates to limited results of nine female Fabry disease patients with eight unique α -Gal A mutations (four responsive and four non-responsive) who were in Phase 2 clinical trials with different dose regimens of migalastat hydrochloride.²⁹⁴ In my opinion, this limited data cannot be extrapolated to a general statement that all Fabry patients with amenable mutations demonstrate greater pharmacodynamic response to migalastat hydrochloride compared to Fabry patients with non-amenable mutations. Dr. Medin also opines that "Giugliani further

²⁹² See generally Benjamin 2016.

²⁹³ Medin Opening Report, ¶ 167 (quoting Giugliani at Abstract); Ex. C at 8-9.

²⁹⁴ Giugliani at Abstract.

discloses categorizing GLA mutations ‘as being amenable or not to migalastat HCl based on an in vitro α -Gal A transfection assay developed in human embryonic kidney (HEK)-293 cells.’”²⁹⁵ Giugliani refers to a HEK-293 cell-based assay that was determined to be unreliable at identifying responsive and non-responsive mutations and further, the assay results as to amenability are only disclosed for the eight mutations at issue in the study, and not generally for all amenable mutations. None of the eight mutations in the study appear in Claim 17 of the ’489 patent. In addition, Giugliani refers to the HEK assay that was determined to be unreliable, including because it was used for enrollment in Amicus’s phase 3 clinical studies, which resulted in the 011 study failing to meet its endpoint for the first six months of data. Thus, it is my opinion that Giugliani does not provide any teaching on the α -Gal A mutations from Claim 17 of the ’489 Patent.

224. Dr. Medin opines that “Wu also discloses α -galactosidase A mutations that cause Fabry disease.”²⁹⁶ As noted above, the HEK-293 cell-based assay in Wu was found to be unreliable in identifying responsive and non-responsive mutations. Further, Wu only discloses data for a limited number of specific mutations from in vitro testing and none of those mutations are in Claim 17 of the ’489 patent. Dr. Medin also opines that “Wu discloses the α -galactosidase A HEK -293 assay amenable mutation Q57L.”²⁹⁷ I disagree, as discussed above with respect to Claim 8 of the ’388 Patent, and this mutation is not in Claim 17 of the ’489 Patent. Further, in my opinion, Wu does not provide any teaching on the α -Gal A mutations from Claim 17 of the ’489 Patent.

²⁹⁵ Medin Opening Report, ¶ 167 (quoting Giugliani at Abstract); Ex. C at 8-9.

²⁹⁶ Medin Opening Report, ¶ 168 (citing Wu at 969-70, Table 1); Ex. C at 8.

²⁹⁷ Medin Opening Report, ¶ 169 (citing Wu at 969-70 (Table 1)); Ex. C at 8.

225. Dr. Medin also opines that “Germain [2012] also discloses α -galactosidase A mutations that cause Fabry disease.”²⁹⁸ This vastly overstates Germain 2012’s disclosures because Germain 2012 merely relates to nine male Fabry disease patients with eight unique α -Gal A mutations, none of which are in Claim 17 of the ’489 Patent. As noted above, Germain 2012 refers to the HEK assay that was determined to be unreliable, including because it was used for enrollment in Amicus’s phase 3 clinical studies, which resulted in the 011 study failing to meet its endpoint for the first six months of data.

226. Dr. Medin next opines that “[i]t was known that mutations in the GLA gene that encode α -galactosidase A (α -Gal A) cause Fabry disease,” and that “[b]y 2011, more than 600 disease-causing mutations in the GLA gene had been identified . . . and by March 2016, more than 800 disease-causing mutations in the GLA gene had been identified”²⁹⁹ In my opinion, the high number of unique GLA mutations that had been discovered adds to the complexity of the methods of treatment with migalastat and supports the nonobviousness of Claim 17. In my opinion, it would not have been obvious to try treatment with migalastat for Fabry patients with the specific mutations of Claim 17 of the ’489 Patent, especially given the unpredictability of whether or not Fabry patients with a given mutation would respond to treatment with migalastat; further, a person of ordinary skill in the art would not have had a reasonable expectation of success with respect to treating Fabry patients that carry the mutations of Claim 17 with migalastat.

227. Dr. Medin opines that “[i]t was well known in the art that migalastat selectively binds and stabilizes α -Gal A, and that a HEK-293 cell-based assay could be used to identify

²⁹⁸ Medin Opening Report, ¶ 169 (citing Germain 2012 at 3, 5, 9); Ex. C at 8.

²⁹⁹ Medin Opening Report, ¶ 170.

mutant forms of α -Gal A that are responsive to migalastat.”³⁰⁰ In my opinion, Dr. Medin has vastly overstated the state of the field at the time the application leading to the ’489 Patent was filed. In fact, the HEK-293 cell-based assay from the ’319 Patent Publication, Wu, Germain 2012, and Giugliani was found to be unable to accurately identify which patients to treat with migalastat. In addition, Benjamin 2016 did not disclose sufficient information about the Migalastat Amenability Assay to identify or determine which mutations are amenable to migalastat treatment. Further, Benjamin 2016 does not disclose treatment of Fabry patients with any of the specific mutations in Claim 17. Indeed, pharmacological chaperones were a relatively new avenue of treatment that was being explored. As of the priority date, there were no FDA approved pharmacological chaperones for any disease, let alone for Fabry disease.³⁰¹ Although there were theories about how migalastat may be able to selectively bind and stabilize α -Gal A in certain situations, it was unknown when this would occur; and the disclosures in the art at the time suggested that it was highly unpredictable which mutated α -Gal A would be stabilized by migalastat. Further, the HEK assay referred to in those references was determined to be unreliable, including because it was used for enrollment in Amicus’s phase 3 clinical studies, which resulted in the 011 study failing to meet its endpoint for the first six months of data.

³⁰⁰ Medin Opening Report, ¶¶ 170, 171.

³⁰¹ See e.g., Keyzor I., et al., (2023) Therapeutic Role of Pharmacological Chaperones in Lysosomal Storage Disorders: A Review of the Evidence and Informed Approach to Reclassification, *Biomolecules* **13**(8):1227 (“The term “pharmacological chaperone therapy” or “PCT” was first coined in 2000 to describe the category of exogenously administered small molecules that restore folding and trafficking defects of misfolded proteins in LSDs. The EMA approved the first commercially available PCT, migalastat (Galafold®; Amicus Therapeutics Inc., Philadelphia, PA, USA), in 2016, for long-term treatment of adults with Fabry disease who have an amenable mutation (i.e., a mutation that is responsive to treatment).”) (internal citation omitted) (ATGAL_10161626 at -627); May 31, 2016, Amicus Therapeutics Announces European Commission Approval for Galafold™ (Migalastat) in Patients with Fabry Disease in European Union (ATGAL_07336052 at -052); Moran, N., (2018) FDA Approves Galafold, a Triumph for Amicus, *Nat. Biotech.* 36:91 (ATGAL_10161450 at -450).

228. Dr. Medin opines that “it would have been obvious for a [person of ordinary skill in the art] to carry out the steps of a known cell assay to identify the naturally-occurring α -galactosidase A mutations recited in at least claim 11.”³⁰² For all of the reasons discussed above, I disagree. Further, Dr. Medin points to no reason why a person of ordinary skill in the art would have found the mutations in Claim 17 of the ’489 Patent in particular and been motivated to test these mutations to treat patients with one of those mutations or any reason why a person of ordinary skill in the art would have had a reasonable expectation of success in doing so.

229. Dr. Medin opines that “[a] [person of ordinary skill in the art] would have been motivated with a reasonable expectation of success to combine the teachings of Wu, Germain 2012, Benjamin (2016), and/or Giugliani, at least because each is directed to the use of migalastat in the treatment of Fabry disease and/or the evaluation of mutations in the α -galactosidase A gene in patients with Fabry disease that inform treatment options for Fabry disease, including treatment with migalastat.”³⁰³ I disagree. In my opinion, a person of ordinary skill in the art would not have combined results or teachings from Benjamin 2016 with those of Wu, Germain 2012, and Giugliani to treat Fabry patients with the mutations of Claim 17 of the ’489 Patent because they would have no reason to do it. More importantly, even if a person of ordinary skill in the art did combine such references, such person of ordinary skill in the art would not be motivated to reach the invention claimed in Claim 17 with any reasonable expectation of success for all of the reasons described above, including, e.g., because none of the mutations at issue in Claim 17 of the ’489 Patent are disclosed in these references as being amenable to migalastat. Dr. Medin also opines that “a [person of ordinary skill in the art] seeking

³⁰² Medin Opening Report, ¶ 171; Ex. C at 8-9.

³⁰³ Medin Opening Report, ¶ 172; Ex. C at 8-10.

to improve upon existing treatments of Fabry disease would have been motivated with a reasonable expectation of success to combine the disclosures of Wu, and/or Germain 2012 in view of Benjamin (2016) and/or Giugliani, and the knowledge of a [person of ordinary skill in the art].”³⁰⁴ He also opines that “a [person of ordinary skill in the art] would have been motivated to combine the teachings of Wu, Germain 2012, Giugliani, and/or Benjamin (2016) because they all have complementary teachings and show consistent outcomes, therefore, a [person of ordinary skill in the art] would also have an expectation of success in doing so.”³⁰⁵ I also disagree with these opinions. Dr. Medin fails to explain exactly which disclosures of Wu, Germain 2012, Benjamin 2016, and Giugliani a person of ordinary skill in the art would combine and why there is a motivation to combine, and why doing so would result in a reasonable expectation of success. Simply saying they have “complementary teachings and show consistent outcomes” does nothing to explain why there would be a reasonable expectation of success. Further, although Dr. Medin mentions the knowledge of a person of ordinary skill in the art, he fails to identify exactly what that knowledge is.

230. With respect to the additional limitations of Claim 17, Dr. Medin opines that “Wu discloses ‘the administration of ‘a dose of 150 mg [migalastat hydrochloride] every other day’ as a potential treatment for Fabry disease.”³⁰⁶ Dr. Medin further opines that Wu “discloses ‘the administration of different [migalastat hydrochloride] doses (50, 150, or 250 mg).’”³⁰⁷ Dr. Medin also opines that Wu discloses that “most mutant forms [of α -Gal A] that were tested at both lower and higher doses showed a ‘good’ response at either dose. This suggests that a single

³⁰⁴ Medin Opening Report, ¶ 172; Ex. C at 8-10.

³⁰⁵ Medin Opening Report, ¶ 173; Ex. C at 8-10.

³⁰⁶ Medin Opening Report, ¶ 177 (citing Wu at 974); Ex. C at 8-9.

³⁰⁷ Medin Opening Report, ¶ 177 (citing Wu at 975); Ex. C at 8-9.

common dose and regimen of AT1001 may be sufficient to mediate a response of the enzyme in vivo for many mutant forms of α -Gal A.”³⁰⁸ Dr. Medin overstates what Wu discloses. Wu actually discloses that:

The degree of consistency found in the current comparison of HEK-293 cell-based and in vivo mutant α -GAL A responses does not necessarily indicate the degree of consistency that would be seen with any particular dose or regimen of [migalastat hydrochloride]. This is because the in vivo α -GAL A responses analyzed here were obtained following different [migalastat hydrochloride] doses (50, 150, or 250 mg) and with various regimens (every other day, twice per day, or every day), according to the different clinical study protocols.³⁰⁹

In my opinion, this is a disclosure of specific doses and dose regimens provided to a limited number of specific Fabry patients with specific mutations. It does not disclose that any such dosages or regimens could be used to treat Fabry patients with other α -Gal A mutation or that a specific dose or regimen is recommended for Fabry patients with the mutations in Claim 17.

231. Dr. Medin opines that Germain 2012 discloses “oral administration of 150 mg migalastat HCl every other day.”³¹⁰ Dr. Medin again overstates this disclosure because like Wu, Germain 2012 relates to treatment of a limited number of specific Fabry patients with specific Fabry mutations at specific doses and dose regimens. It does not disclose that a specific dose or regimen is recommended for Fabry patients with the mutations in Claim 17.

232. Dr. Medin opines that Giuliani discloses “the oral administration of migalastat hydrochloride at doses of 50 mg, 150 mg, and 250 mg every other day (QOD) to females with Fabry disease.”³¹¹ Dr. Medin again overstates this disclosure because like Wu and Germain 2012, Giuliani relates to treatment of a limited number of specific Fabry patients with specific

³⁰⁸ Medin Opening Report, ¶ 177 (citing Wu at 975), Ex. C at 8.

³⁰⁹ Wu at 975.

³¹⁰ Medin Opening Report, ¶ 178 (citing Germain 2012 at Abstract); Ex. C at 8-9.

³¹¹ Medin Opening Report, ¶ 178 (citing Giuliani at Abstract); Ex. C at 8-9.

Fabry mutations at specific doses and dose regimens. It does not disclose that a specific dose or regimen is recommended for Fabry patients with the mutations in Claim 17.

233. Dr. Medin opines that Benjamin 2016 discloses “administration of 150 mg migalastat HCl.”³¹² Dr. Medin’s reliance on Benjamin 2016 is also misplaced because Benjamin 2016 does not disclose treatment of Fabry patients with the mutations in Claim 17 of the ’489 Patent, nor does it disclose use of 150 mg every other day with respect to these mutations. In fact, Benjamin 2016 does not identify any amenable mutation based on the Migalastat Amenability Assay.

234. Dr. Medin opines that “a [person of ordinary skill in the art] would have been motivated to combine the teachings of Wu, Germain 2012, Giugliani, and/or Benjamin (2016) for this dosing because they all have complementary teachings and show consistent outcomes, therefore, a [person of ordinary skill in the art] would also have an expectation of success in doing so.”³¹³ I disagree. Dr. Medin fails to explain exactly which disclosures of Wu, Germain 2012, Benjamin 2016, and Giugliani a person of ordinary skill in the art would combine and why there is a motivation to combine, and why doing so would result in a reasonable expectation of success. Simply saying they have “complementary teachings and show consistent outcomes” does nothing to explain why there would be a reasonable expectation of success. Further, although Dr. Medin mentions the knowledge of a person of ordinary skill in the art, he fails to identify exactly what that knowledge is.

235. It is unclear what combination(s) Dr. Medin is relying upon for his analysis of Claim 17. Because Dr. Medin’s obviousness combinations are unclear, I reserve the right to

³¹² Medin Opening Report, ¶ 178 (citing Benjamin 2016 at 4); Ex. C at 9.

³¹³ Medin Opening Report, ¶ 178; Ex. C at 8-10.

supplement my opinions based on any additional and/or clarifying opinions that Dr. Medin renders with respect to Claim 17. Further, Dr. Medin fails to identify what he is using as his base reference, how he is modifying it and what reference he is modifying it with, and why a person of ordinary skill in the art would have been motivated to modify the reference or have had a reasonable expectation of success in such a combination. Dr. Medin more generally fails to explain how he is combining the prior art references and why, in his opinion, such references would cause a person of ordinary skill in the art to reach the claimed invention. In addition, he generally fails to acknowledge the fact that the prior art references he relies on do not disclose treating Fabry patients with the specific mutations in Claim 17, and he fails to explain how a person of ordinary skill in the art would reach such a method of treatment for those specific mutations based on the references he relies upon.

236. Dr. Medin opines that “claim 11 is invalid under 35 U.S.C. § 103 as obvious over Wu and/or Germain 2012 in view of Benjamin (2016), and/or Giugliani, and the knowledge of a [person of ordinary skill in the art].”³¹⁴ I understand Claim 11 is not asserted. To the extent Dr. Medin intends to refer to asserted Claim 17, for all the reasons discussed herein, in my opinion, Dr. Medin has failed to prove that Claim 17 is obvious. Based on my review of the prior art references and the disclosures cited, in my opinion, Claim 17 is not obvious and there is no motivation to combine the references with any reasonable expectation of success in reaching the invention of Claim 17. Dr. Medin generally fails to acknowledge the fact that the prior art references he relies on do not disclose treating Fabry patients with the specific mutations in Claim 17 and he fails to explain how a person of ordinary skill in the art would reach such a method of treatment for those specific mutations based on the references he relies upon, why a

³¹⁴ Medin Opening Report, ¶ 179; Ex. C at 8-9.

person of ordinary skill in the art would combine them, and why such a person would have a reasonable expectation of success in doing so.

2. Claim 23

237. Claim 23 of the '489 Patent (bolded below) depends from Claim 22, which depends from Claim 11. The claim language is:

11. A method of treating Fabry disease, the method comprising administering migalastat to a patient in need thereof, wherein the patient has an α -galactosidase A protein comprising a HEK assay amenable mutation selected from the group consisting of A13T, N34T, M42K, L54F, P60T, E87D, L89F, Y123C, H125L, I133M, K140T, F145S, P146R, Y152H, D165G, p.M187_S188dup, V199G, M208R, I219L, N224T, Q250R, G261C, G271D, M284V, I303F, D322N, G325R, K326N, G334E, E358Q, E358D, G361E, G375E, T412N and M421V.

22. The method of claim 11, wherein the mutation is selected from the group consisting of: L54F, L89F, K140T and G334E.

23. The method of claim 22, wherein the patient is administered about 150 mg of migalastat hydrochloride every other day.

238. Based on my review of Dr. Medin's report, it is unclear what combinations Dr. Medin asserts for Claim 23. Dr. Medin lists only the following combinations in the summary of his opinions:

- 1) The '319 patent publication in view of Lockhart '093 and the knowledge of a person of ordinary skill in the art;
- 2) Wu, Germain [2012], Benjamin 2016, and/or Giugliani and the knowledge of a person of ordinary skill in the art;
- 3) Wu and/or Germain [2012] in view of Benjamin 2016 and/or Giugliani and the knowledge of a person of ordinary skill in the art.³¹⁵

239. Regarding the first combination—the '319 Patent Publication in view of Lockhart '093 and the knowledge of a person of ordinary skill in the art—Dr. Medin did not identify what knowledge a person of ordinary skill in the art would have had that is relevant to

³¹⁵ Medin Opening Report, ¶ 13.

this combination or why a person of ordinary skill in the art would have been motivated to use that knowledge to modify what is disclosed in the '319 Patent Publication.

240. Regarding the second combination—Wu, Germain 2012, Benjamin, and/or Giugliani, and the knowledge of a person of ordinary skill in the art—it is unclear exactly which of those references he is combining and how those references are being combined. Dr. Medin discusses each of the four references individually before alleging in a conclusory fashion that they could be combined with no explanation of how they would be combined.³¹⁶ Dr. Medin again failed to identify what knowledge a person of ordinary skill in the art would have had that is relevant to this combination or why a person of ordinary skill in the art would have been motivated to use that knowledge to modify what is disclosed in the references cited by Dr. Medin.

241. Regarding the third combination—Wu and/or Germain 2012 in view of Benjamin 2016 and/or Giugliani and the knowledge of a person of ordinary skill in the art—it is unclear exactly which of those references he is combining and how those references are being combined. Like with the second combination, Dr. Medin discusses each of the four references individually before alleging in a conclusory fashion that they would be combined, with no explanation of how they would be combined or why a person of ordinary skill in the art would combine them.³¹⁷

³¹⁶ See Medin Opening Report, ¶ 189 (“A POSA [person of ordinary skill in the art] would have been motivated with a reasonable expectation of success to combine the teachings of Wu, Germain 2012, Benjamin (2016), and/or Giugliani, at least because each is directed to guiding the use of migalastat in the treatment of Fabry disease and/or the evaluation of mutations in the α -galactosidase A gene in patients with Fabry disease in order to guide treatment options for Fabry disease, including treatment with migalastat.”).

³¹⁷ See Medin Opening Report, ¶ 189 (“A POSA [person of ordinary skill in the art] seeking to improve upon the existing treatments of Fabry disease would have been motivated with a reasonable expectation of success to combine the disclosures of Wu, and/or Germain 2012 in view of Benjamin (2016) and/or Giugliani, and the knowledge of a POSA [person of ordinary skill in the art].”).

Again, Dr. Medin failed to identify what knowledge a person of ordinary skill in the art would have had that is relevant to this combination or why a person of ordinary skill in the art would have been motivated to use that knowledge to modify what is disclosed in the references cited by Dr. Medin.

242. In my opinion, as discussed further below, Dr. Medin's combinations do not disclose the limitations of Claim 23 and do not render Claim 23 obvious.

243. I incorporate by reference my analysis of Claim 11 from above, which I analyzed for Claim 17, and which applies equally to Claim 23. I address the remaining limitations of Claim 23 below.

a) Asserted Combination 1: the '319 Patent Publication in view of Lockhart '093 and the Knowledge of a Person of Ordinary Skill in the Art

244. To support his obviousness analysis for Claim 23, Dr. Medin cites to Proposed Claim 10 of the '319 Patent Publication to argue that methods for treating Fabry with migalastat was known.³¹⁸ Dr. Medin further opines that the '319 Patent Publication "discloses a method of treating Fabry disease by administering migalastat to a patient."³¹⁹ I disagree. The '319 Patent Publication discloses results of an in vitro HEK assay with respect to specific mutations and that some, but not all, mutations are responsive to migalastat. It does not teach a general method of treatment for Fabry disease by administering migalastat to any Fabry patient.

245. Dr. Medin relies on Proposed Claim 10 of the '319 Patent Publication, which states:

10. A method of treating a patient diagnosed with Fabry disease which comprises administering to the patient a therapeutically effective dose of 1-deoxygalactonorjirimycin, wherein the patient expresses a mutant α -

³¹⁸ Medin Opening Report, ¶ 182.

³¹⁹ Medin Opening Report, ¶ 184.

galactosidase A selected from the group consisting of the α -galactosidase A mutations A257D, A257G, A257P, A291T, A292T, A307T, **A309P**, **A352V**, A368T, A73V, A97V, C174G, C174R, C56F, C56Y, D165H, D313G, D322E, D55V, E203V, F169S, G171R, G183A, G183V, G258R, G258V, G261D, G325S, G360D, G360S, G85D, G85M, I117S, I198T, I239T, I253T, I289S, I319T, I359T, K185E, K308N, L166G, L16H, L19P, L243W, L36F, L36S, L372P, L403S, L54P, M290I, M290L, M296L, M296T, M42L, M42R, M76T, M96I, N53L, P205S, P293T, P409A, P409T, P60L, Q107L, Q250P, Q312R, Q321H, Q321L, R301G, **R356G**, S238N, S247C, T282A, T410I, V339E, W162G, W349S, Y152C, Y184C, Y200C, Y207H and Y216C.³²⁰

From this list of over eighty mutations, Dr. Medin then focuses on only a few cherry-picked mutations based on their amino acid positions, namely A309P, A352V, and R356G (bolded and underlined above). None of the mutations in Claim 23 are at any of these three amino acid positions.

246. Dr. Medin also opines that the '319 Patent Publication "discloses that the mutations A20P, I242N, A309P, A352V, R356G, and R356W are responsive to migalastat, i.e., they are HEK assay amenable mutations."³²¹ Dr. Medin then opines that "[a] [person of ordinary skill in the art] would know that amino acid positions 20, 242, 309, 352, and 356 in α -galactosidase A have missense mutations in Fabry patients and would therefore be motivated to explore other mutations at the same amino acid positions."³²²

247. As a preliminary matter, Dr. Medin seems to be mixing up the concepts of responsiveness in the HEK assay described in the '319 Patent Publication with the concept of HEK assay amenable mutations described in the '489 Patent. In drawing this inappropriate parallel, Dr. Medin is using the '489 Patent's disclosures and thus is using hindsight to support his obviousness arguments. The assay in the '319 Patent Publication is different than the assay

³²⁰ Medin Opening Report, ¶ 182; '319 Patent Publication, Proposed Claim 10, Ex. C at 11.

³²¹ Medin Opening Report, ¶ 182, Ex. C at 11.

³²² Medin Opening Report, ¶ 182.

in the '489 Patent and Claim 23 refers to a “HEK assay amenable mutation” in the Migalastat Amenability Assay—the assay described in the '489 Patent, not the assay described in the '319 Patent Publication.

248. Further, I disagree with Dr. Medin’s opinions for several other reasons. *First*, as described above in the technology background (§VI), Fabry disease is difficult to diagnose and treat because there are many different α -Gal A mutations that cause Fabry disease. Each mutation may cause different symptoms, ultimately causing different presentations of the disease in each patient. A disclosure that a patient with one of the α -Gal A mutations, for example, as in Proposed Claim 10 of the '319 Patent Publication, could be treated with migalastat does not inform a person of ordinary skill in the art whether other Fabry disease patients with different α -Gal A mutations could be treated with migalastat. Further, the '319 Patent Publication discloses examples of an α -Gal A mutation at a specific amino acid location being responsive to treatment with migalastat and a different mutation at the same location is not.³²³ In fact, the '319 Patent Publication itself recognizes that there is no way to predict whether a Fabry patient with a specific mutation will be responsive or not to treatment with migalastat prior to testing.³²⁴ This remains true even if the mutation occurs at the same position in the α -Gal A protein. For example, the '319 Patent Publication discloses that the L16H, N34K, R112H, N224S, A352V mutations are responsive to treatment with migalastat but the L16P, N34S, R112C, R112S,

³²³ '319 Patent Publication, at Fig. 17 (showing responsive GLA mutations L16H, N34K, R112H, N224S, A352V); '319 Patent Publication, Fig. 18 (showing non-responsive GLA mutations L16P, N34S, R112C, R112S, N224D, A352P, A352D).

³²⁴ See, e.g., '319 Patent Publication, ¶ 0150 (“DGJ-responsive and non-responsive mutant forms did not appear to be located to particular regions or domains on the α -Gal A protein structure.”); '319 Patent Publication, ¶ 0146 (“No significant correlation between response and location on the protein sequence of a mutation was observed, suggesting that responsive as well as non-responsive mutations are distributed widely across the entire protein.”).

N224D, A352P, A352D mutations are non-responsive to treatment with migalastat.³²⁵ Thus, a person of ordinary skill in the art would not be motivated based on the disclosures of the '319 Patent Publication to look for other α -Gal A mutations at the same amino acid position as a mutation that is reported as responsive to treatment with migalastat in the '319 Patent Publication. The '319 Patent Publication, including Proposed Claim 10, does not include any of the α -Gal A mutations in Claim 23 of the '489 Patent and therefore does not disclose or render obvious treatment of Fabry patients with the specific α -Gal A mutations of Claim 23 with migalastat. Just because a specific mutation at a particular amino acid position results in an α -Gal A protein that is responsive to treatment with migalastat as measured by the HEK assay discussed in the '319 Patent Publication does not allow a person of ordinary skill in the art to predict which other mutations at the same amino acid position may be responsive.

249. **Second**, none of the A20P, I242N, A309P, A352V, R356G, and R356W mutations are included in Claim 23 of the '489 Patent. There is no other reason Dr. Medin points to that would lead a person of ordinary skill in the art to treat Fabry patients with one of the specific mutations in Claim 23 with migalastat based on the disclosure in the '319 Patent Publication that different mutations are responsive to treatment with migalastat. In addition, none of the mutations in Claim 23 of the '489 Patent are at any of these amino acid positions.

250. **Third**, the '319 Patent Publication discloses that some α -Gal A mutations are responsive to treatment with migalastat and some are not.³²⁶ In addition, the '319 Patent Publication references hundreds of missense mutations and there are many different positions for possible mutations. Dr. Medin cherry picks these amino acid positions for a select few of the

³²⁵ '319 Patent Publication, at Figs. 17-18.

³²⁶ See, e.g., '319 Patent Publication, at Fig. 17 and 18.

hundreds of mutations based on hindsight. Dr. Medin presents no reason why a person of ordinary skill in the art would look to these few mutations rather than the hundreds of others in the '319 Patent Publication.

251. Further, Dr. Medin also opines that the '319 Patent Publication discloses that the A13P, Q57L, P146S, and I242F mutations were generated by site-directed mutagenesis and that the “specification of the '489 patent identifies these mutations as HEK assay amenable mutations.”³²⁷ Further, Dr. Medin further opines that “[a]s being HEK assay amenable is an inherent property of the identified mutations, this claim limitation would have inherently existed in the prior art.”³²⁸ It is not clear to me what Dr. Medin is suggesting and Dr. Medin ignores that none of the mutations he points to are in Claim 23 and none of the mutations in Claim 23 are in the '319 Patent Publication.

252. Dr. Medin opines that “[a] [person of ordinary skill in the art] would have been motivated to identify patients with GLA mutations suffering from Fabry disease, determine if these mutations are HEK amenable mutations, and once a mutation such as A13P, Q57L, P146S, or I242F, would be determined to be an HEK assay amenable mutation, to administer migalastat to patients having these mutations.”³²⁹ For the reasons explained above with respect to Claim 8 of the '388 Patent, I also disagree with this opinion. Further, this argument is especially inapplicable to Claim 23 of the '489 Patent because none of A13P, Q57L, P146S or I242F are in Claim 23 of the '489 Patent. Further, the '319 Patent Publication reports these four mutations as non-responsive to migalastat and a person of ordinary skill in the art would not be motivated to

³²⁷ Medin Opening Report, ¶ 183.

³²⁸ Medin Opening Report, ¶ 183.

³²⁹ Medin Opening Report, ¶ 184, Ex. C at 11.

treat such patients with migalastat with any reasonable expectation of success. Dr. Medin has provided no reason why a person of ordinary skill in the art would have re-tested these mutations or how to re-test in a different assay or why they would have had a reasonable expectation of success in treating patients with these four mutations with migalastat. In addition, the '319 Patent Publication discusses a HEK assay that was found to be unreliable in identifying Fabry patients who could benefit from treatment with migalastat. The inability of the assay discussed in the '319 Patent Publication to accurately predict whether a mutation was responsive or non-responsive to migalastat was demonstrated by the failure to reach the primary endpoint in the six-month data for Amicus's phase 3 clinical trial, which used this assay for enrollment.

253. Dr. Medin then opines that “[c]laim 22 would have been obvious over the '319 patent publication in view of the knowledge of a [person of ordinary skill in the art].”³³⁰ As an initial matter, Dr. Medin did not identify this alleged combination in the summary of his opinions (Medin Opening Report, ¶ 13), and it is unclear if Dr. Medin is asserting this as a standalone combination. Further, I understand from counsel that Claim 22 is not asserted and I have been asked to respond only as to Claim 23. To the extent Dr. Medin intends to refer to Claim 23, I disagree. Although Dr. Medin refers to the '319 Patent Publication in combination with the knowledge of a person of ordinary skill in the art, Dr. Medin does not identify any “knowledge of a [person of ordinary skill in the art]” that he is using as part of the obviousness analysis in this claim. Thus, in my opinion, Dr. Medin has also failed to show that Claim 23 of the '489 Patent is obvious over the '319 Patent Publication in combination with the knowledge of a person of ordinary skill in the art.

³³⁰ Medin Opening Report, ¶ 184.

254. With respect to the additional limitations of Claim 23, Dr. Medin opines that “Lockhart discloses administering the hydrochloride salt of DGJ (i.e., migalastat) to participants at a specific dose level of 150 mg every other day.”³³¹ In my opinion, Dr. Medin overstates the disclosures in Lockhart ’093. Lockhart ’093 does not disclose that a dose of 150 mg every other day will work for all α -Gal A mutations or even for all amenable mutations. Further, Lockhart ’093 does not disclose that 150 mg every other day is an effective dose for Fabry patients with any of the mutations in Claim 23. Dr. Medin relies upon Lockhart ’093’s discussion of modeling of doses related to IFG and the disclosure that such model could be applicable to DGJ.³³² This theoretical model does not provide a motivation to treat a Fabry patient with a specific dosage, especially in light of the many other dose regimens discussed in Lockhart ’093, including in the Examples 4-6 that Dr. Medin cites.³³³

255. Dr. Medin opines that “[a] [person of ordinary skill in the art] would have been aware of the 150 mg every other day dosing of migalastat to treat Fabry Disease and its effectiveness from at least Lockhart ’093, and therefore would have been motivated to rely on this teaching to arrive at the 150 mg every other day dosing.”³³⁴ Dr. Medin also opines that “[a] [person of ordinary skill in the art] would further have had an expectation of success with this dosing given the teachings of Lockhart ’093.”³³⁵ I disagree with these opinions. Lockhart ’093 does not disclose that 150 mg every other day is an effective dose for all Fabry patients or for all Fabry patients with an amenable mutation. Nor does Lockhart ’093 even suggest that 150 mg

³³¹ Medin Opening Report, ¶ 191 (citing Lockhart ’093, ¶ 0151, Exs. 4-6), Ex. C at 12.

³³² Lockhart ’093, ¶¶ 0142, 0151.

³³³ Lockhart ’093, ¶¶ 0142, 0151; *see also supra* § VIII.A.5.

³³⁴ Medin Opening Report, ¶ 192, Ex. C at 12.

³³⁵ Medin Opening Report, ¶ 192.

every other day is the preferred dose and dose regimen of migalastat hydrochloride for any Fabry patient. Lockhart '093 relies of theoretical dosing models and preliminary data for enrollment of phase 2 studies related to migalastat hydrochloride where a number of different doses and dose regimens were used.³³⁶ A person of ordinary skill in the art would have understood Lockhart '093 to be a preliminary investigation into dosing of pharmacological chaperones like migalastat hydrochloride and not some definitive reference of the proper dose of migalastat hydrochloride for all Fabry patients, as Dr. Medin suggests.

256. Dr. Medin then opines that “claim 23 of the '489 patent would have been obvious over the '319 patent publication in view of Lockhart and the knowledge of a [person of ordinary skill in the art].”³³⁷ I disagree. In my opinion, the disclosures of the '319 Patent Publication and in view of Lockhart '093 and the knowledge of a person of ordinary skill in the art do not render obvious Claim 23. Further, although Dr. Medin refers to the '319 Patent Publication in view of Lockhart '093 and the knowledge of a person of ordinary skill in the art, Dr. Medin does not identify any “knowledge of a [person of ordinary skill in the art]” that he is using as part of the obviousness analysis in this claim. Thus, in my opinion, Dr. Medin has failed to show that Claim 23 of the '489 Patent is obvious over the '319 Patent Publication in view of Lockhart '093 and the knowledge of a person of ordinary skill in the art. Dr. Medin generally fails to acknowledge the fact that the prior art references he relies on do not disclose treating Fabry patients with the specific mutations in Claim 23 and he fails to explain how a person of ordinary skill in the art would reach such a method of treatment for those specific mutations based on the

³³⁶ See Lockhart '093, Exs. 4-6.

³³⁷ Medin Opening Report, ¶ 191.

references he relies upon, why a person a person of ordinary skill would combine them, and why such a person would have a reasonable expectation of success in doing so.

b) Asserted Combination 2: Wu, Germain 2012, Giugliani, and/or Benjamin 2016 and the Knowledge of a Person of Ordinary Skill in the Art;

and

Asserted Combination 3: Wu and/or Germain 2012 in View of Benjamin 2016 and/or Giugliani and the Knowledge of a Person of Ordinary Skill in the Art

257. For the additional limitations of Claim 23, with respect to the vague combinations of Wu, Germain 2012, Giugliani, and/or Benjamin 2016, Dr. Medin opines that “it was known in the art that Fabry disease is characterized by mutations to the GLA gene, which encodes the enzyme α -galactosidase A and that migalastat stabilizes α -Gal A.”³³⁸ Dr. Medin overstates the state of the art because it was not known at the time of the invention of Claim 23 which α -Gal A mutations could be stabilized by migalastat or how to determine whether such stabilization would occur. Dr. Medin further opines that “[a] [person of ordinary skill in the art] would have been motivated to assess whether a patient has mutant forms of α -Gal A that are amenable to migalastat to improve methods for treating Fabry disease in a patient using migalastat or a salt thereof, with a reasonable expectation of success.”³³⁹ There are a very large number of possible mutant forms of α -Gal A and Dr. Medin provides no reason why a skilled artisan would look for the mutant forms in Claim 23. Further, Dr. Medin points to no reliable way to determine whether any such mutant forms are amenable. He also provides no reason a skilled artisan

³³⁸ Medin Opening Report, ¶ 185.

³³⁹ Medin Opening Report, ¶ 185, Ex. C at 11.

would have had a reasonable expectation of success in reaching the claimed invention given the state of the art.

258. Dr. Medin opines that “it was well known that a HEK-293 cell-based assay could be used to identify mutant forms of α -Gal A that are responsive to migalastat” and points to disclosures in Germain 2012, Wu, Benjamin, and Giuliani.³⁴⁰ In my opinion, this is not an accurate description of the state of the field at the time of the invention of Claim 23 of the ’489 Patent. Wu, Germain 2012, and Giuliani disclose a research-based HEK assay. Benjamin on the other hand discusses the development of another HEK assay. Dr. Medin is conflating these two distinct assays in his analysis. The HEK-293 cell-based assay used in Germain 2012, Wu, and Giuliani could not accurately predict whether a mutation was responsive or non-responsive to migalastat and the disclosures in Benjamin do not identify to a person of ordinary skill in the art which mutations are being discussed with respect to the Migalastat Amenability Assay.³⁴¹ The inability of the assay discussed in Germain 2012, Wu, and Giuliani to accurately predict whether a mutation was responsive or non-responsive to migalastat was demonstrated by the failure to reach the primary endpoint in the six-month data for Amicus’s phase 3 clinical trial, which used this assay for enrollment.

259. Dr. Medin opines that “[a] [person of ordinary skill in the art] would have known that HEK-293 cells were first described in the late 1970s and as early as 1992, these cells were used for transfection and analyses of variant proteins and thus would have been a known tool in the toolbox of a [person of ordinary skill in the art].”³⁴² Although use of a HEK cell-based assay

³⁴⁰ Medin Opening Report, Ex. C at 11.

³⁴¹ See generally Benjamin 2016.

³⁴² Medin Opening Report, ¶ 185.

was known, what was not known was how to use such an assay to reliably identify amenable and nonamenable mutations.

260. Dr. Medin cites Germain 2012's disclosure that "[a]n in vitro α -Gal A gene transfection assay, specific for each individual mutation, was developed in HEK-293 cells" that was "used to define if a patient carrying a GLA mutation was amenable to migalastat HCl."³⁴³ I disagree. Even this disclosure recognizes that the treatment would be "genotype-specific" and thus cannot be applied to all Fabry patients. This is because Germain 2012 discloses results from only a limited number of Fabry patients with specific mutations, none of which overlap with those in Claim 23.³⁴⁴ As such, a person of ordinary skill in the art would understand that certain patients would not benefit from treatment with migalastat hydrochloride. Absent specific disclosure that a patient with a specific mutation would benefit from migalastat treatment, a skilled artisan would not be motivated to treat such patients with migalastat. Thus, it is my opinion that Germain 2012 does not provide any teaching on how to treat Fabry patients with the disclosed α -Gal A mutations of Claim 23 of the '489 Patent.

261. Dr. Medin also opines that Germain 2012 also discloses "mutations considered amenable to migalastat HCl."³⁴⁵ This vastly overstates Germain 2012's disclosures because Germain 2012 merely relates to nine male Fabry disease patients with eight unique α -Gal A mutations, none of which are in Claim 23 of the '489 Patent. As noted above, Germain 2012 refers to the HEK assay that was determined to be unreliable, including because it was used for

³⁴³ Medin Opening Report, ¶ 185.

³⁴⁴ See Germain 2012 at Abstract (describing results from two phase 2 studies of nine males with Fabry disease).

³⁴⁵ Medin Opening Report, ¶ 185 (citing Germain 2012 at 5), Ex. C at 11.

enrollment in Amicus's phase 3 clinical studies, which resulted in the 011 study failing to meet its endpoint for the first six months of data.

262. Dr. Medin opines that Wu discloses that "migalastat hydrochloride (AT1001, GR181413A) [is] currently in clinical development to evaluate its safety and efficacy as a potential treatment for Fabry disease."³⁴⁶ I disagree. Dr. Medin overreads Wu. Wu's teachings are directed to a certain subset of Fabry patients rather than all Fabry patients, and certainly not all Fabry patients with amenable mutations. For example, Wu states that "a pharmacological chaperone may be a viable treatment for Fabry disease, serving as an alternative to enzyme replacement therapy *for some patients*."³⁴⁷ Dr. Medin also points to Wu's disclosure of a "cell-based assay in cultured HEK-293 cells to identify mutant forms of α -Gal-A that are responsive to [migalastat HCl]."³⁴⁸ The HEK-293 cell-based assay in Wu was found to be unreliable in identifying responsive and non-responsive mutations. Further, Wu only discloses data for a limited number of specific mutations from in vitro testing and none of those mutations are disclosed in Claim 23 of the '489 patent.

263. Dr. Medin cites Giuliani's disclosure that "[p]atients with amenable mutations seem to demonstrate greater pharmacodynamic response to migalastat HCl compared to patients with non-amenable mutations."³⁴⁹ Dr. Medin is taking this disclosure out of context. Giuliani's disclosure relates to limited results of nine female Fabry disease patients with eight unique α -Gal A mutations (four responsive and four non-responsive) who were in Phase 2

³⁴⁶ Medin Opening Report, ¶ 187 (quoting Wu at 965), Ex. C at 11.

³⁴⁷ Wu at 965 (emphasis added).

³⁴⁸ Medin Opening Report, ¶ 187 (quoting Wu at Abstract), Ex. C at 11.

³⁴⁹ Medin Opening Report, ¶ 188 (quoting Giuliani at Abstract), Ex. C at 11.

clinical trials with different dose regimens of migalastat hydrochloride.³⁵⁰ In my opinion, this limited data cannot be extrapolated to a general statement that all Fabry patients with amenable mutations demonstrate greater pharmacodynamic response to migalastat hydrochloride compared to Fabry patients with non-amenable mutations. Dr. Medin also opines that “Giugliani further discloses categorizing GLA mutations ‘as being amenable or not to migalastat HCl based on an in vitro α -Gal A transfection assay developed in human embryonic kidney (HEK)-293 cells.’”³⁵¹ Giugliani refers to a HEK-293 cell-based assay that was determined to be unreliable at identifying responsive and non-responsive mutations and further, the assay results as to amenability are only disclosed for the eight mutations at issue in the study, and not generally for all amenable mutations. None of the eight mutations in the study appear in Claim 23 of the ’489 patent. In addition, Giugliani refers to the HEK assay that was determined to be unreliable, including because it was used for enrollment in Amicus’s phase 3 clinical studies, which resulted in the 011 study missing its endpoint for the first six months of data. Thus, it is my opinion that Giugliani does not provide any teaching on the α -Gal A mutations from Claim 23 of the ’489 Patent.

264. Dr. Medin also cites to Benjamin 2016, which he asserts “discloses the identification of amenable mutant forms of α -Gal A using a GLP-validated HEK-293 cell-based assay (Migalastat Amenability Assay)” and that this assay has a “high predictive value in identifying [Fabry Disease] patients who show a pharmacodynamic response to oral administration of migalastat.”³⁵² I disagree. In my opinion, Benjamin 2016 does not disclose the

³⁵⁰ See Giugliani at Abstract.

³⁵¹ Medin Opening Report, ¶ 188.

³⁵² Medin Opening Report, ¶ 186 (citing Benjamin 2016 at 7), Ex. C at 11.

identification of amenable mutant forms of α -Gal A using the Migalastat Amenability Assay. Notably, there are no specific mutations mentioned at all on the page that Dr. Medin cites, or anywhere in the poster.³⁵³ In my opinion, the disclosure that the Migalastat Amenability Assay is highly predictive of pharmacodynamic response to oral administration of migalastat does not provide a person of ordinary skill in the art with a motivation to treat any specific Fabry disease patient with migalastat. In addition, Benjamin 2016 does not disclose treatment of Fabry patients with any of the specific mutations in Claim 23. Thus, it is my opinion that Benjamin 2016 does not provide any teaching on the α -Gal A mutations from Claim 23 of the '489 Patent.

265. Dr. Medin opines that “[a] [person of ordinary skill in the art] would have been motivated to combine the teachings of Wu, Germain 2012, Benjamin (2016), and Giugliani, in view of the knowledge of a [person of ordinary skill in the art], at least because each is directed to guiding the use of migalastat in the treatment of Fabry disease and/or the evaluation of mutations in the α -galactosidase A gene in patients with Fabry disease in order to guide treatment options for Fabry disease, including treatment with migalastat.”³⁵⁴ I disagree. In my opinion, a person of ordinary skill in the art would not have combined results or teachings from Benjamin 2016 with those of Wu, Germain 2012, and Giugliani to treat Fabry patients with the specific mutations of Claim 23 of the '489 Patent because they would have no reason to do it. More importantly, even if a person of ordinary skill in the art did combine such references, such person of ordinary skill in the art would not be motivated to reach the invention claimed in Claim 23 with any reasonable expectation of success for all of the reasons described above, including,

³⁵³ See Benjamin 2016 at 7.

³⁵⁴ Medin Opening Report, ¶ 189, Ex. C at 11, 13.

e.g., because none of the mutations at issue in Claim 23 are disclosed in these references as being amenable to migalastat.

266. Dr. Medin also opines that “a [person of ordinary skill in the art] seeking to improve upon existing treatments of Fabry disease would have been motivated with a reasonable expectation of success to combine the disclosures of Wu, and/or Germain 2012, in view of Benjamin (2016), and in view of the knowledge of a [person of ordinary skill in the art].”³⁵⁵ I also disagree with these opinions. Dr. Medin fails to explain exactly which disclosures of Wu, Germain 2012, and Benjamin 2016 a person of ordinary skill in the art would combine and why there is a motivation to combine, and why doing so would result in a reasonable expectation of success. Further, although Dr. Medin mentions knowledge of a person of ordinary skill in the art, he fails to identify what that knowledge is. Dr. Medin also opines that “[a] [person of ordinary skill in the art] would have been motivated to combine the teachings of Wu, Germain [2012], Giuliani, and/or Benjamin (2016) because they all have complementary [sic] teachings and showing consistent outcomes, therefore, a POSA would also have an expectation of success in doing so.”³⁵⁶ I also disagree with these opinions. Dr. Medin fails to explain exactly which disclosures of Wu, Germain 2012, Benjamin 2016, and Giuliani a person of ordinary skill in the art would combine and why there is a motivation to combine, and why doing so would result in a reasonable expectation of success. Simply saying they have “complementary teachings and show consistent outcomes” does nothing to explain why there would be a reasonable expectation of success. Moreover, although Dr. Medin mentions knowledge of a person of ordinary skill in the art, he fails to identify exactly what that knowledge is.

³⁵⁵ Medin Opening Report, ¶ 189.

³⁵⁶ Ex. C at 13.

267. With respect to the additional limitations of Claim 23, Dr. Medin opines that “Wu discloses ‘the administration of ‘a dose of 150 mg [migalastat hydrochloride] every other day’ as a potential treatment for Fabry disease.”³⁵⁷ Dr. Medin further opines that Wu “discloses ‘the administration of different [migalastat hydrochloride] doses (50,150, or 250 mg) and with various regimens.”³⁵⁸ Dr. Medin also opines that Wu discloses that “most mutant forms [of α -Gal A] that were tested at both lower and higher doses showed a ‘good’ response at either dose. This suggests that a single common dose and regimen of AT1001 may be sufficient to mediate a response of the enzyme in vivo for many mutant forms of α -Gal A.”³⁵⁹ Dr. Medin overstates what Wu discloses. Wu actually discloses that:

The degree of consistency found in the current comparison of HEK-293 cell-based and in vivo mutant α -GAL A responses does not necessarily indicate the degree of consistency that would be seen with any particular dose or regimen of [migalastat hydrochloride]. This is because the in vivo α -GAL A responses analyzed here were obtained following different [migalastat hydrochloride] doses (50, 150, or 250 mg) and with various regimens (every other day, twice per day, or every day), according to the different clinical study protocols.³⁶⁰

In my opinion, this is a disclosure of specific doses and dose regimens provided to a limited number of specific Fabry patients with specific mutations. It does not disclose that any such dosages or regimens could be used to treat Fabry patients with other α -Gal A mutation or that a specific dose or regimen is recommended for Fabry patients with the mutations in Claim 23.

268. Dr. Medin opines that Germain 2012 discloses “oral administration of 150 mg migalastat HCl once every other day.”³⁶¹ Dr. Medin again overstates this disclosure because like

³⁵⁷ Medin Opening Report, ¶ 193 (citing Wu at 974), Ex. C at 12.

³⁵⁸ Medin Opening Report, ¶ 193.

³⁵⁹ Medin Opening Report, ¶ 193 (citing Wu at 975), Ex. C at 12.

³⁶⁰ Wu at 975.

³⁶¹ Medin Opening Report, ¶ 194 (citing Germain 2012 at Abstract), Ex. C at 12.

Wu, Germain 2012 relates to treatment of a limited number of specific Fabry patients with specific Fabry mutations at specific doses and dose regimens. It does not disclose that a specific dose or regimen is recommended for Fabry patients with the mutations in Claim 23.

269. Dr. Medin opines that Giugliani discloses “the oral administration of migalastat hydrochloride at doses of 50 mg, 150 mg, and 250 mg every other day (QOD) to females with Fabry disease.”³⁶² Dr. Medin again overstates this disclosure because like Wu and Germain 2012, Giugliani relates to treatment of a limited number of specific Fabry patients with specific Fabry mutations at specific doses and dose regimens. It does not disclose that a specific dose or regimen is recommended for Fabry patients with the mutations in Claim 23.

270. Dr. Medin opines that Benjamin 2016 discloses “administration of 150 mg migalastat HCl.”³⁶³ Dr. Medin’s reliance on Benjamin 2016 is also misplaced because Benjamin 2016 does not disclose treatment of Fabry patients with the mutations in Claim 23 of the ’489 Patent, nor does it disclose use of 150 mg every other day with respect to these mutations. In fact, Benjamin 2016 does not identify any amenable mutation based on the Migalastat Amenability Assay.

271. It is unclear what combination(s) Dr. Medin is even relying upon for his analysis of Claim 23. Because Dr. Medin’s obviousness combinations are unclear I reserve the right to supplement my opinions based on any additional and/or clarifying opinions that Dr. Medin renders with respect to Claim 23. Further, Dr. Medin fails to identify what he is using as his base reference, how he is modifying it and what reference he is modifying it with, and why a person of ordinary skill in the art would be motivated to modify the reference or have had a reasonable

³⁶² Medin Opening Report, ¶ 194 (citing Giugliani at Abstract), Ex. C at 12.

³⁶³ Medin Opening Report, ¶ 194 (citing Benjamin 2016 at 4), Ex. C at 12.

expectation of success in such a combination. Dr. Medin more generally fails to explain how he is combining the prior art references and how and why, in his opinion, such references would cause a person of ordinary skill in the art to reach the claimed invention. In addition, he generally fails to acknowledge the fact that the prior art references he relies on do not disclose treating Fabry patients with the specific mutations in Claim 23 and he fails to explain how a person of ordinary skill in the art would reach such a method of treatment for those specific mutations based on the references he relies upon.

272. Dr. Medin opines that “claim 23 would have been obvious over Wu and/or Germain 2012 in view of Benjamin (2016), and/or Giugliani, and the knowledge of a [person of ordinary skill in the art].”³⁶⁴ For all the reasons discussed herein, in my opinion, Dr. Medin has failed to prove that Claim 23 is obvious. Based on my review of the prior art references and the disclosures cited, in my opinion, Claim 23 is not obvious and there is no motivation to combine the references with any reasonable expectation of success in reaching the invention of Claim 23. Dr. Medin generally fails to acknowledge the fact that the prior art references he relies on do not disclose treating Fabry patients with the specific mutations in Claim 23 and he fails to explain how a person of ordinary skill in the art would reach such a method of treatment for those specific mutations based on the references he relies upon, why a person of ordinary skill in the art would combine them, and why such a person would have a reasonable expectation of success in doing so.

³⁶⁴ Medin Opening Report, ¶ 194.

E. Claim 9 of the '490 Patent

273. As an initial matter, it is unclear to me what combination of references Dr. Medin is using for his prior art combinations for this claim. Dr. Medin opines in the summary of his opinions that:

[b]y way of example, the asserted claims are rendered obvious by the following combinations:

- 1) The '319 Patent Publication in view of Lockhart '093 and the knowledge of a [person of ordinary skill in the art]
- 2) Wu, Germain [2012], Benjamin, and/or Giugliani and the knowledge of a [person of ordinary skill in the art]
- 3) Wu and/or Germain [2012] in view of Benjamin and/or Giugliani and the knowledge of a [person of ordinary skill in the art.]³⁶⁵

Dr. Medin seems to imply that there could be additional combinations, but he does not explicitly disclose what those additional combinations might be. Accordingly, I will respond to the opinions and specific combinations that Dr. Medin actually analyzed in his report, and I reserve the right to respond to any additional combinations should Dr. Medin later render an opinion as to such combinations.

274. Moreover, this list results in dozens of possible combinations of prior art references. Dr. Medin does not actually analyze each of these combinations in his report, and thus it is unclear what teaching(s) Dr. Medin proposes to take from each reference and why a person of ordinary skill in the art would have been motivated to combine those elements or teachings with a reasonable expectation of success. Instead, Dr. Medin's only obviousness analysis is him analyzing six references, the '319 Patent Publication, Lockhart '093, Wu, Germain 2012, Benjamin 2016, and Giugliani individually without specifying how to combine

³⁶⁵ Medin Opening Report, ¶ 13.

them within the context of his proposed obviousness combinations let alone why a person of ordinary skill in the art would be motivated to combine those references in such a way. For example, Dr. Medin fails to explain what reference he is starting with and how he is modifying such reference with the other prior art references.³⁶⁶ Accordingly, I will respond to the opinions that Dr. Medin actually included in his report regarding the disclosed combinations, and I reserve the right to respond to any additional opinions about those combinations should Dr. Medin later render any opinion about what and how the specific references are to be combined and/or the motivation to combine or modify such specific references.

1. Claim 9

275. Asserted Claim 9 of the '490 Patent (bolded below) depends from Claim 7, which depends from Claim 1. The claim language is:

1. A method of treating Fabry disease, the method comprising administering migalastat to a patient in need thereof, wherein the patient has an α -galactosidase A protein comprising a HEK assay amenable mutation selected from the group consisting of: I242F, G334E, N34D and p.V254del.

7. The method of claim 1, wherein the patient is administered about 150 mg of migalastat hydrochloride every other day.

9. The method of claim 7, wherein the mutation is I242F.

276. Based on my review of Dr. Medin's report, it is unclear what combinations Dr. Medin asserts for Claim 9. Dr. Medin lists only the following combinations in the summary of his opinions:

- 1) The '319 Patent Publication in view of Lockhart '093 and the knowledge of a person of ordinary skill in the art;

³⁶⁶ See generally Medin Opening Report, § IX.D (element by element analysis of the asserted claim of the '490 patent); see also Medin Opening Report, Exhibit C (claim chart including list of citations to each of the six asserted prior art references without separating by combination).

- 2) Wu, Germain [2012], Benjamin 2016, and/or Giugliani and the knowledge of a person of ordinary skill in the art;
- 3) Wu and/or Germain [2012] in view of Benjamin 2016 and/or Giugliani and the knowledge of a person of ordinary skill in the art.³⁶⁷

277. Regarding the first combination—the '319 Patent Publication in view of Lockhart '093 and the knowledge of a person of ordinary skill in the art—Dr. Medin did not identify what knowledge a person of ordinary skill in the art would have had that is relevant to this combination or why a person of ordinary skill in the art would have been motivated to use that knowledge to modify what is disclosed in the '319 Patent Publication.

278. Regarding the second combination—Wu, Germain 2012, Benjamin, and/or Giugliani, and the knowledge of a person of ordinary skill in the art—it is unclear exactly which of those references he is combining and how those references are being combined. Dr. Medin discusses each of the four references individually before alleging in a conclusory fashion that they could be combined with no explanation of how they would be combined.³⁶⁸ Dr. Medin again failed to identify what knowledge a person of ordinary skill in the art would have had that is relevant to this combination or why a person of ordinary skill in the art would have been motivated to use that knowledge to modify what is disclosed in the references cited by Dr. Medin.

³⁶⁷ Medin Opening Report, ¶ 13.

³⁶⁸ See Medin Opening Report, ¶ 217 (“In addition, a POSA [person of ordinary skill in the art] would have been motivated to combine the teachings of Wu, Germain [2012], Giugliani and/or Benjamin (2016) because they all have complementary teachings and show consistent outcomes, therefore, a POSA [person of ordinary skill in the art] would also have an expectation of success in doing so.”); *see also* Medin Opening Report, ¶ 230 (“A POSA [person of ordinary skill in the art] would have been motivated with a reasonable expectation of success to combine the teachings of Wu, Germain 2012, Benjamin (2016), and/or Giugliani, at least because each is directed to the use of migalastat in the treatment of Fabry disease and/or the evaluation of mutations in the α -galactosidase A gene in patients with Fabry disease that inform treatment options for Fabry disease, including treatment with migalastat.”).

279. Regarding the third combination—Wu and/or Germain 2012 in view of Benjamin 2016 and/or Giugliani and the knowledge of a person of ordinary skill in the art—it is unclear exactly which of those references he is combining and how those references are being combined. Like with the second combination, Dr. Medin discusses each of the four references individually before alleging in a conclusory fashion that they would be combined, with no explanation of how they would be combined or why a person of ordinary skill in the art would combine them.³⁶⁹ Again, Dr. Medin failed to identify what knowledge a person of ordinary skill in the art would have had that is relevant to this combination or why a person of ordinary skill in the art would have been motivated to use that knowledge to modify what is disclosed in the references cited by Dr. Medin.

280. In my opinion, as discussed further below, Dr. Medin’s combinations do not disclose the limitations of Claim 9 and do not render Claim 9 obvious.

a) Asserted Combination 1: the ’319 Patent Publication in view of Lockhart ’093 and the Knowledge of a Person of Ordinary Skill in the Art

281. To support his obviousness opinions, Dr. Medin cites to Proposed Claim 10 of the ’319 Patent Publication to argue that methods for treating Fabry with migalastat was known.³⁷⁰ Dr. Medin further opines that the ’319 Patent Publication “discloses a method of treating Fabry disease by administering migalastat to a patient.”³⁷¹ I disagree. The ’319 Patent Publication discloses results of an in vitro HEK assay with respect to specific mutations.

³⁶⁹ See Medin Opening Report, ¶ 230 (“Furthermore, a POSA [person of ordinary skill in the art] seeking to improve upon the existing treatments of Fabry disease would have been motivated with a reasonable expectation of success to combine the disclosures of Wu, and/or Germain 2012 in view of Benjamin (2016) and/or Giugliani, and the knowledge of a POSA [person of ordinary skill in the art].”).

³⁷⁰ ’319 Patent Publication, Proposed Claim 10.

³⁷¹ Medin Opening Report, ¶¶ 202, 222.

282. Dr. Medin relies on Proposed Claim 10 of the '319 Patent Publication, which states:

10. A method of treating a patient diagnosed with Fabry disease which comprises administering to the patient a therapeutically effective dose of 1-deoxygalactonorjirimycin, wherein the patient expresses a mutant α -galactosidase A selected from the group consisting of the α -galactosidase A mutations A257D, A257G, A257P, A291T, A292T, A307T, **A309P**, **A352V**, A368T, A73V, A97V, C174G, C174R, C56F, C56Y, D165H, D313G, D322E, D55V, E203V, F169S, G171R, G183A, G183V, G258R, G258V, G261D, G325S, G360D, G360S, G85D, G85M, I117S, I198T, I239T, I253T, I289S, I319T, I359T, K185E, K308N, L166G, L16H, L19P, L243W, L36F, L36S, L372P, L403S, L54P, M290I, M290L, M296L, M296T, M42L, M42R, M76T, M96I, N53L, P205S, P293T, P409A, P409T, P60L, Q107L, Q250P, Q312R, Q321H, Q321L, R301G, **R356G**, S238N, S247C, T282A, T410I, V339E, W162G, W349S, Y152C, Y184C, Y200C, Y207H and Y216C.³⁷²

From this list of over eighty mutations, Dr. Medin then focuses on only a few cherry-picked mutations based on their amino acid positions.³⁷³

283. Similarly, Dr. Medin also opines that the '319 Patent Publication “discloses that the mutations A20P, I242N, A309P, A352V, R356G, and R356W are responsive to migalastat, i.e., they are HEK assay amenable mutations.”³⁷⁴ Dr. Medin then opines that “a [person of ordinary skill in the art] would know that amino acid positions 20, 242, 309, 352, and 356 on α -galactosidase A have missense mutations in Fabry patients and would therefore be motivated to explore other mutations at the same amino acid positions.”³⁷⁵

284. As a preliminary matter, Dr. Medin seems to be mixing up the concepts of responsiveness in the HEK assay described in the '319 Patent Publication with the concept of

³⁷² Medin Opening Report, ¶ 197, Ex. C at 14; '319 Patent Publication, Proposed Claim 10.

³⁷³ Medin Opening Report, ¶ 197 (calling attention to A309P, A352V, and R356G, which are not the amino acid position at issue in Claim 9 of the '490 Patent), Ex. C at 16; *see supra* analysis of Claim 8.

³⁷⁴ Medin Opening Report, ¶¶ 200, 220, Ex. C at 14 & 16.

³⁷⁵ Medin Opening Report, ¶¶ 200, 220.

HEK assay amenable mutations described in the '490 Patent. In drawing this inappropriate parallel, Dr. Medin is using the '490 Patent's disclosures and thus is using hindsight to support his obviousness arguments. The assay in the '319 Patent Publication is different than the assay in the '490 Patent and Claim 9 refers to a "HEK assay amenable mutation" in the Migalastat Amenability Assay—the assay described in the '490 Patent, not the assay described in the '319 Patent Publication.

285. Further, I disagree with Dr. Medin's opinions for several other reasons. *First*, as described above in the technology background (§VI), Fabry disease is difficult to diagnose and treat because there are many different α -Gal A mutations that cause Fabry disease. Each mutation may cause different symptoms, ultimately causing different presentations of the disease in each patient. A disclosure that a patient with one of the α -Gal A mutations, for example, as in Proposed Claim 10 of the '319 Patent Publication, could be treated with migalastat does not inform a person of ordinary skill in the art whether other Fabry disease patients with different α -Gal A mutations could be treated with migalastat. Further, the '319 Patent Publication discloses examples of an α -Gal A mutation at a specific amino acid location being responsive to treatment with migalastat and a different mutation at the same location is not.³⁷⁶ In fact, the '319 Patent Publication itself recognizes that there is no way to predict with a Fabry patient with a specific mutation will be responsive or not to treatment with migalastat prior to testing.³⁷⁷ This remains

³⁷⁶ '319 Patent Publication, at Fig. 17 (showing responsive GLA mutations L16H, N34K, R112H, N224S, A352V); '319 Patent Publication, Fig. 18 (showing non-responsive GLA mutations L16P, N34S, R112C, R112S, N224D, A352P, A352D).

³⁷⁷ See, e.g., '319 Patent Publication, ¶ 0150 ("DGJ-responsive and non-responsive mutant forms did not appear to be located to particular regions or domains on the α -Gal A protein structure."); '319 Patent Publication, ¶ 0146 ("No significant correlation between response and location on the protein sequence of a mutation was observed, suggesting that responsive as well as non-responsive mutations are distributed widely across the entire protein.").

true even if the mutation occurs at the same position in the α -Gal A protein. For example, the '319 Patent Publication discloses that the L16H, N34K, R112H, N224S, A352V mutations are responsive to treatment with migalastat but the L16P, N34S, R112C, R112S, N224D, A352P, A352D mutations are non-responsive to treatment with migalastat.³⁷⁸ Thus, a person of ordinary skill in the art would not be motivated based on the disclosures of the '319 Patent Publication to look for other α -Gal A mutations at the same amino acid position as a mutation that is reported as responsive to treatment with migalastat in the '319 Patent Publication.

286. **Second**, none of the A20P, I242N, A309P, A352V, R356G, and R356W mutations are included in Claim 9 of the '490 Patent. There is no other reason Dr. Medin points to that would lead a person of ordinary skill in the art to treat Fabry patients with one of the specific mutations in Claim 9 with migalastat based on the disclosure in the '319 Patent Publication that different mutations are responsive to treatment with migalastat.

287. **Third**, the '319 Patent Publication discloses that some α -Gal A mutations are responsive to treatment with migalastat and some are not.³⁷⁹ In addition, the '319 Patent Publication references hundreds of missense mutations and there are many different positions for possible mutations. Dr. Medin cherry picks these amino acid positions for a select few of the hundreds of mutations based on hindsight. Dr. Medin presents no reason why a person of ordinary skill in the art would look to these few mutations rather than the hundreds of others in the '319 Patent Publication.

³⁷⁸ See '319 Patent Publication, at Figs. 17-18.

³⁷⁹ '319 Patent Publication, at Figs. 17-18.

288. Further, Dr. Medin also opines that the '319 Patent Publication "discloses that the α -galactosidase A mutation D322N was generated by site-directed mutagenesis."³⁸⁰ Dr. Medin also opines that "[t]he specification of the '490 Patent identifies [the D322N] mutation[] as HEK assay amenable mutations."³⁸¹ This mutation is not in Claim 9 of the '490 Patent, so it is unclear why Dr. Medin points to it here. To the extent Dr. Medin intended to refer to the I242F mutation, this would be misleading because the '319 Patent Publication identifies this mutation as non-responsive.³⁸² In my opinion, Dr. Medin is using hindsight, and the teachings of the '490 Patent, for his obviousness analysis with respect to Claim 9 of the '490 Patent. I understand that the disclosures of the '490 Patent on this mutation's amenability should not be used to support the proposition that the invention of the '490 Patent is obvious when the prior art discloses that such mutation is non-amenable. In fact, although the '319 Patent Publication does discuss the I242F mutation, which appears in Claim 9 of the '490 Patent, the '319 Patent Publication discourages a person of skill in the art from treating Fabry patients with the I242F mutation with migalastat. For example, for Fabry disease patients with an I242F mutation, the '319 Patent Publication discloses that such patients should not be treated with migalastat, because according to the results obtained by the HEK assay described in the '319 Patent Publication, these mutations are non-responsive to treatment with migalastat.³⁸³ The '319 Patent Publication discloses—based on the results of the in vitro activity assay described in the '319 Patent

³⁸⁰ Medin Opening Report, ¶¶ 201, 221.

³⁸¹ Medin Opening Report, ¶¶ 201, 221.

³⁸² '319 Patent Publication, Figs. 1A, 18, ¶¶ 0026, 0043, 0177.

³⁸³ '319 Patent Publication, at Figs. 1A, 18, ¶¶ 0026, 0043, 0177.

Publication—that Fabry patients with an I242F mutation are non-responsive to migalastat.³⁸⁴

The '319 Patent Publication also teaches that Fabry patients with a non-responsive α -Gal A mutation should not be treated with migalastat.³⁸⁵ The '319 Patent Publication states:

In a further embodiment, the invention relates to a method of treating a patient diagnosed with Fabry disease by administering to the patient a therapeutically effective dose of 1-deoxygalactonorigirimycin, or a similar pharmacological chaperone to a patient that expresses a mutation in α -galactosidase A, ***with the proviso that the mutation is not a nonresponsive mutation*** and/or the mutation is not a mutation in which no enzyme is expressed.³⁸⁶

In my opinion, a person of ordinary skill in the art would not be motivated to treat Fabry disease patients with the I242F mutation based on the disclosures of the '319 Patent Publication. Rather, the '319 Patent Publication discourages a skilled artisan, or teaches away, from treating such Fabry patients with migalastat. A person of ordinary skill in the art would know that treating Fabry patients with α -Gal A mutations that are non-responsive to migalastat is not the most beneficial treatment for a patient and a person of ordinary skill in the art would not be motivated to treat patients with non-responsive mutations with migalastat and would not have a reasonable expectation of success in doing so. Further, it would be unethical for a physician to treat a patient with a drug that the physician knows is not the optimal drug for that patient, and thereby prevent them from receiving the most beneficial treatment for their specific disease.

289. Dr. Medin fails to acknowledge further prior art references that suggest treating a Fabry patient who has a non-amenable mutation with migalastat would not be beneficial. Thus, it is my opinion that Dr. Medin fails to provide any reason why a person of ordinary skill in the

³⁸⁴ See, e.g., '319 Patent Publication, at Fig. 18. For example, the '319 Patent Publication discloses the I242F mutation is a “[n]on-responsive GLA mutation[.]” See, e.g., '319 Patent Publication, at Figs. 1A, 18, ¶¶ 0026, 0043, 0177.

³⁸⁵ '319 Patent Publication, ¶ 0177.

³⁸⁶ '319 Patent Publication, ¶0025 (emphasis added).

art would be motivated to treat such Fabry patients with a reasonable expectation of success upon reading the '319 Patent Publication. Dr. Medin also fails to provide any reason why a person of ordinary skill in the art would be motivated to search for a different answer than the one provided in the '319 Patent Publication on whether a Fabry patient with an I242F mutation would respond to treatment with migalastat.

290. Dr. Medin further opines that “[a]s being HEK assay amenable is an inherent property of the identified mutations, this claim limitation would have inherently existed in the prior art.”³⁸⁷ It is not clear to me what Dr. Medin is suggesting. As already discussed, none of the prior art that Dr. Medin relies upon teaches the HEK assay of the '490 Patent; nor do they, either alone or in combination, teach that a Fabry patient with the specific mutation of Claim 9 of the '490 Patent may be amenable to migalastat treatment. To the contrary, the explicit teachings of the '319 Patent Publication that the I242F mutations is “non-responsive” to treatment with migalastat would have taught a skilled person in the art away from using migalastat for treating these patients.

291. Dr. Medin opines that “[a] [person of ordinary skill in the art] would have been motivated to identify patients with GLA mutations suffering from Fabry disease, determine if these mutations are HEK amenable mutations, and once a mutation such as A13P, Q57L, P146S, or I242F, would be determined to be an HEK assay amenable mutation, to administer migalastat to patients having these mutations.”³⁸⁸ For the reasons explained above, I also disagree with this opinion. For example, with respect to the specific mutation in Claim 9 of the '490 Patent, a person of ordinary skill in the art using the HEK assay described in the '319 Patent Publication

³⁸⁷ Medin Opening Report, ¶¶ 201, 221.

³⁸⁸ Medin Opening Report, ¶¶ 202, 222, Ex. C at 14-17.

would have found the I242F mutation to be non-responsive to migalastat and thus would not have been motivated to treat such patients with migalastat with any reasonable expectation of success. Dr. Medin has provided no reason why a person of ordinary skill in the art would have re-tested this mutation or how to re-test in a different assay or why they would have had a reasonable expectation of success in treating patients with the mutations in Claim 9 with migalastat. In addition, the '319 Patent Publication discusses a HEK assay that was found to be unreliable in identifying Fabry patients who could benefit from treatment with migalastat. The inability of the assay discussed in the '319 Patent Publication to accurately predict whether a mutation was responsive or non-responsive to migalastat was demonstrated by the failure to reach the primary endpoint in the six-month data for Amicus's phase 3 clinical trial, which used this assay for enrollment.

292. Dr. Medin opines that “Lockhart discloses administering the hydrochloride salt of DGJ (i.e., migalastat) to participants at a specific dose level of 150 mg every other day.”³⁸⁹ In my opinion, Dr. Medin overstates the disclosures in Lockhart '093. Lockhart '093 does not disclose that a dose of 150 mg every other day will work for all α -Gal A mutations or even for all amenable mutations. Further, Lockhart '093 does not disclose that 150 mg every other day is an effective dose for Fabry patients with the mutation in Claim 9. Dr. Medin relies upon Lockhart '093's discussion of modeling of doses related to IFG and the disclosure that such model could be applicable to DGJ.³⁹⁰ This theoretical model does not provide a motivation to treat a Fabry patient with a specific dosage, especially in light of the many other dose regimens discussed in Lockhart '093, including in the Examples 4-6 that Dr. Medin cites.³⁹¹

³⁸⁹ Medin Opening Report, ¶ 214 (citing Lockhart '093, ¶ 0151, Exs. 4-6), Ex. C at 15.

³⁹⁰ Lockhart '093, ¶¶ 0142, 0151.

³⁹¹ Lockhart '093, ¶¶ 0142, 0151; *see also supra* § VIII.A.5.

293. Dr. Medin opines that “[a] [person of ordinary skill] in the art would have been aware of the 150 mg every other day dosing of migalastat to treat Fabry Disease and its effectiveness from at least Lockhart ’093, and therefore would have been motivated to rely on this teaching to arrive at the 150 mg every other day dosing.”³⁹² Dr. Medin also opines that “[a] [person of ordinary skill in the art] would further have had an expectation of success with this dosing given the teachings of Lockhart ’093.”³⁹³ I disagree with these opinions. Lockhart ’093 does not disclose that 150 mg every other day is an effective dose for all Fabry patients or for all Fabry patients with an amenable mutation. Nor does Lockhart ’093 even suggest that 150 mg every other day is the preferred dose and dose regimen of migalastat hydrochloride for any Fabry patient. Lockhart ’093 relies on theoretical dosing models and preliminary data for enrollment of phase 2 studies related to migalastat hydrochloride where a number of different doses and dose regimens were used.³⁹⁴ A person of ordinary skill in the art would have understood Lockhart ’093 to be a preliminary investigation into dosing of pharmacological chaperones like migalastat hydrochloride and not some definitive reference of the proper dose of migalastat hydrochloride for all Fabry patients, as Dr. Medin suggests.

294. Dr. Medin then opines that “claims 1 and 7 of the ’489 [sic] patent are obvious over the ’319 patent publication in view of Lockhart and the knowledge of a [person of ordinary skill in the art]” and that “Claim 9 is invalid as obvious for all the reasons that claims 1 and 7 are obvious.”³⁹⁵ I understand that Claims 1 and 7 of the ’490 Patent are not asserted, and I have been asked to respond only as to Claim 9. With respect to Claim 9, I disagree. In my opinion,

³⁹² Medin Opening Report, ¶ 215, Ex. C at 15-16.

³⁹³ Medin Opening Report, ¶ 215, Ex. C at 16.

³⁹⁴ See Lockhart ’093, Exs.4-6.

³⁹⁵ Medin Opening Report, ¶¶ 214, 219.

the disclosures of the '319 Patent Publication in view of Lockhart '093 and the knowledge of a person of ordinary skill in the art do not render obvious Claim 9. Further, although Dr. Medin refers to the '319 Patent Publication in view of Lockhart '093 and the knowledge of a person of ordinary skill in the art, Dr. Medin does not identify any “knowledge of a [person of ordinary skill in the art]” that he is using as part of the obviousness analysis in this claim. Thus, in my opinion, Dr. Medin has failed to show that Claim 9 of the '490 Patent is obvious over the '319 Patent Publication in view of Lockhart '093 and the knowledge of a person of ordinary skill in the art. Dr. Medin generally fails to acknowledge the fact that the prior art references he relies on do not disclose treating Fabry patients with the specific mutations in Claim 9 and he fails to explain how a person of ordinary skill in the art would reach such a method of treatment for those specific mutations based on the references he relies upon, why a person of ordinary skill in the art would combine them, and why such a person would have a reasonable expectation of success in doing so.

b) Asserted Combination 2: Undisclosed Combination of Wu, Germain 2012, Giugliani, and/or Benjamin 2016 and the Knowledge of a Person of Ordinary Skill in the Art;

and

Asserted Combination 3: Wu and/or Germain 2012 in View of Benjamin 2016 and/or Giugliani and the Knowledge of a Person of Ordinary Skill in the Art

295. With respect to these combinations, Dr. Medin opines that “it was well known that a HEK-293 cell-based assay could be used to identify mutant forms of α -Gal A that are responsive to migalastat” and points to disclosures in Germain 2012, Wu, Benjamin, and Giugliani.³⁹⁶ In my opinion, this is not an accurate description of the state of the field at the time

³⁹⁶ Medin Opening Report, ¶¶ 203-204, 223-224.

of the invention of Claim 9 of the '490 Patent. Wu, Germain 2012, and Giugliani disclose a research-based HEK assay. Benjamin on the other hand discusses the development of another HEK assay. Dr. Medin is conflating these two distinct assays in his analysis. The HEK-293 cell-based assay used in Germain 2012, Wu, and Giugliani could not accurately predict whether a mutation was responsive or non-responsive to migalastat and the disclosures in Benjamin do not identify to a person of ordinary skill in the art which mutations are being discussed with respect to the Migalastat Amenability Assay.³⁹⁷ The inability of the assay discussed in Germain 2012, Wu, and Giugliani to accurately predict whether a mutation was responsive or non-responsive to migalastat was demonstrated by the failure to reach the primary endpoint in the six-month data for Amicus's phase 3 clinical trial, which used this assay for enrollment.

296. Dr. Medin opines that "Germain 2012 also discloses α -galactosidase A mutations that cause Fabry disease."³⁹⁸ Dr. Medin further opines that "Germain [2012] further discloses mutations considered amenable to migalastat HCl."³⁹⁹ This vastly overstates Germain 2012's disclosures because Germain 2012 merely relates to nine male Fabry disease patients with eight unique α -Gal A mutations, none of which are in Claim 9 of the '490 Patent. As noted above, Germain 2012 refers to the HEK assay that was determined to be unreliable, including because it was used for enrollment in Amicus's phase 3 clinical studies, which resulted in the 011 study failing to meet its endpoint for the first six months of data.

297. Dr. Medin also points to Germain 2012's disclosures that "[a]n in vitro α -GAL-A gene transfection assay, specific for each individual mutation, was developed in HEK-293 cells"

³⁹⁷ See generally Benjamin 2016.

³⁹⁸ Medin Opening Report, ¶¶ 207, 227 (citing Germain 2012 at 3, 5, 9), Ex. C at 14-16.

³⁹⁹ Medin Opening Report, ¶ 203 (citing Germain 2012 at 5).

and that this was “used to define if a patient carrying a GLA mutation was amenable to migalastat HCl,” and Dr. Medin asserts that “Germain 2012 further discloses mutations considered amenable to migalastat HCl.”⁴⁰⁰ In my opinion, Dr. Medin is ignoring the context of such disclosures and, as a result, is vastly overstating Germain’s disclosures. The HEK-293 cell-based assay discussed in Germain 2012 could not accurately predict whether a mutation is amenable to migalastat. Further, Germain 2012 only relates to nine male Fabry patients, with eight unique mutations, none of which are in Claim 9 of the ’490 Patent and Germain 2012 notes that the HEK assay testing was done retrospectively. Germain 2012 does not disclose all mutations considered amenable to migalastat nor does it disclose a reliable way to identify all such mutations. Thus, it is my opinion that Germain 2012 does not provide any teaching on the α -Gal A mutations from Claim 9 of the ’490 Patent.

298. Dr. Medin opines that Germain 2012 discloses that “[m]igalastat HCl is a candidate pharmacological chaperone that provides a novel genotype-specific treatment for [Fabry disease].”⁴⁰¹ I disagree. Even this disclosure recognizes that the treatment would be “genotype-specific” and thus cannot be applied to all Fabry patients. Germain 2012 discloses results from only a limited number of Fabry patients with specific mutations, none of which is the I242F mutation that is specifically recited in Claim 9 of the ’490 Patent.⁴⁰² As such, a person of ordinary skill in the art would understand that certain patients would not benefit from treatment with migalastat hydrochloride. Absent specific disclosure that a patient with a specific mutation would benefit from migalastat treatment, a skilled artisan would not be motivated to

⁴⁰⁰ Medin Opening Report, ¶¶ 203, 223 (citing Germain 2012 at 4-5), Ex. C 14-16.

⁴⁰¹ Medin Opening Report, ¶ 198 (quoting Germain 2012, Abstract), Ex. C 14-16.

⁴⁰² See Germain 2012 at Abstract (describing results from two phase 2 studies of nine males with Fabry disease).

treat such patients with migalastat. Thus, it is my opinion that Germain 2012 does not provide any teaching on how to treat Fabry patients with the disclosed GLA mutations from Claim 9 of the '490 Patent.

299. Dr. Medin opines that “Wu also discloses α -galactosidase A mutations that cause Fabry disease.”⁴⁰³ Dr. Medin also points to Wu’s disclosure of a “cell-based assay in cultured HEK-293 cells to identify mutant forms of α -GALA that are responsive to [migalastat HCl].”⁴⁰⁴ The HEK-293 cell-based assay in Wu was found to be unreliable in identifying responsive and non-responsive mutations. Further, Wu only discloses data for a limited number of specific mutations from in vitro testing and none of those mutations are in Claim 9 of the '490 Patent. Dr. Medin also opines that “Wu discloses the α -galactosidase A HEK -293 assay amenable mutation Q57L.”⁴⁰⁵ Claim 9 does not include the mutation Q57L and, therefore, Dr. Medin’s reliance on the disclosures in Wu Table 1 is misplaced. Thus, it is my opinion that Wu does not provide any teaching on the α -Gal A mutation from Claim 9 of the '490 Patent.

300. Dr. Medin also opines that Wu discloses that “migalastat hydrochloride (AT1001, GR181413A) [is] currently in clinical development to evaluate its safety and efficacy as a potential treatment for Fabry disease” and that “AT1001 (migalastat hydrochloride, 1-deoxygalactonojirimycin) is a pharmacological chaperone for α -Gal A that is in Phase 3 clinical development as a potential therapy for Fabry disease.”⁴⁰⁶ I disagree. Dr. Medin overreads Wu. Wu’s teachings are directed to a certain subset of Fabry patients rather than all Fabry patients, and certainly not all Fabry patients with amenable mutations. For example, Wu states that “a

⁴⁰³ Medin Opening Report, ¶¶ 206, 226 (citing Wu at 969-70, Table 1), Ex. C. 14-16.

⁴⁰⁴ Medin Opening Report, ¶¶ 203, 223 (quoting Wu at Abstract).

⁴⁰⁵ Medin Opening Report, ¶¶ 207, 227 (citing Wu at 969-70 (Table 1)).

⁴⁰⁶ Medin Opening Report, ¶ 198 (quoting Wu at 965, 974).

pharmacological chaperone may be a viable treatment for Fabry disease, serving as an alternative to enzyme replacement therapy *for some patients*.”⁴⁰⁷ Wu also recognizes that not all Fabry patients benefit from treatment with migalastat.⁴⁰⁸ Wu also discloses that “[f]urther evaluation of the utility of the HEK-293 cell-based assay for Fabry patient selection for treatment with AT1001 [migalastat hydrochloride] is ongoing.”⁴⁰⁹ In my opinion, a person of ordinary skill in the art would understand this disclosure to mean that Wu is limited to specific Fabry patients in certain Amicus’s phase 2 clinical trials.⁴¹⁰ In addition, although Wu mentions Phase 3 clinical trials, it does not disclose what mutations are being studied in those trials, or whether any such mutations can be treated with migalastat. Further, a skilled artisan would have understood that the initial data from those phase 3 clinical studies was reported by Amicus as “not meet[ing] statistical significance.”⁴¹¹ As such, Wu does not provide reliable methods of treating Fabry patients, even for the mutations explicitly discussed in the reference, and the disclosures cannot be used to extrapolate any methods of treatment for Fabry patients who are not discussed in the reference. Thus, it is my opinion that Wu does not provide any teaching on how to treat Fabry patients with the α -Gal A mutation from Claim 9 of the ’490 Patent.

301. Dr. Medin cites Giugliani’s disclosure that “[p]atients with amenable mutations seemed to demonstrate greater pharmacodynamic response to migalastat HCl compared to

⁴⁰⁷ Wu at 965 (emphasis added).

⁴⁰⁸ Wu at 975.

⁴⁰⁹ Wu at 976.

⁴¹⁰ Wu at Table 2 (discussing FAB-CL-201, FAB-CL-202, and FAB-CL-203 trial data).

⁴¹¹ Amicus Website, Press Release dated Feb. 15, 2013, available at <https://ir.amicusrx.com/news-releases/news-release-details/amicus-therapeutics-presents-additional-6-month-results-phase-3>.

patients with non-amenable mutations.”⁴¹² Dr. Medin also opines that “Giugliani further discloses, ‘migalastat HCl was generally well tolerated and, in patients with amenable mutations, resulted in GL-3 substrate reduction in urine and some kidney cell types.’”⁴¹³ Dr. Medin is taking these disclosures out of context. Giugliani’s disclosure relates to limited results of nine female Fabry disease patients with eight unique α -Gal A mutations (four responsive and four non-responsive) who were in Phase 2 clinical trials with different dose regimens of migalastat hydrochloride.⁴¹⁴ In my opinion, this limited data cannot be extrapolated to a general statement that all Fabry patients with amenable mutations demonstrate greater pharmacodynamic response to migalastat hydrochloride compared to Fabry patients with non-amenable mutations. Dr. Medin also opines that “Giugliani further discloses categorizing GLA mutations ‘as being amenable or not to migalastat HCl based on an in vitro α -Gal A transfection assay developed in human embryonic kidney (HEK)-293 cells.’”⁴¹⁵ Like German and Wu, Giugliani refers to a HEK-293 cell-based assay that was determined to be unreliable at identifying responsive and non-responsive mutations and further, the assay results as to amenability are only disclosed for the eight mutations at issue in the study, and not generally for all amenable mutations. None of the eight mutations in the study appears in Claim 9 of the ’490 Patent. In addition, Giugliani refers to the HEK assay that was determined to be unreliable, including because it was used for enrollment in Amicus’s phase 3 clinical studies, which resulted in the 011 study missing its endpoint for the first six months of data. Thus, it is my opinion that Giugliani does not provide any teaching on the single α -Gal A mutation, I242F, from Claim 9 of the ’490 Patent.

⁴¹² Medin Opening Report, ¶¶ 205, 225 (quoting Giugliani at Abstract), Ex. C at 14-16.

⁴¹³ Medin Opening Report, ¶¶ 205, 225 (quoting Giugliani at 91).

⁴¹⁴ See Giugliani at Abstract.

⁴¹⁵ Medin Opening Report, ¶¶ 205, 225 (quoting Giugliani at Abstract).

302. Dr. Medin also opines that Giugliani discloses of the “evaluation of ‘the safety and pharmacodynamics of migalastat hydrochloride, an investigational pharmacological chaperone given orally every other day (QOD) to females with FD.’”⁴¹⁶ I disagree. Giugliani discloses specific results related to “nine females with [Fabry disease].”⁴¹⁷ As such, a person of ordinary skill in the art would not understand such disclosure could be extracted to all Fabry disease patients, regardless of their specific α -Gal A mutation.⁴¹⁸ Thus, it is my opinion that Giugliani does not provide any teaching on how to treat Fabry patients with the α -Gal A mutations from Claim 9 of the ’490 Patent.

303. Dr. Medin also relies on Benjamin 2016. Dr. Medin opines that “Benjamin (2016) discloses the identification of amenable mutant forms of α -Gal A using a GLP-validated HEK-293 cell-based assay (Migalastat Amenability Assay) and that ‘the Migalastat Amenability Assay and amenable mutation criteria have high predictive value in identifying [Fabry Disease] patients who show a pharmacodynamic response to oral administration of migalastat.’”⁴¹⁹ I disagree. In my opinion, Benjamin 2016 does not disclose the identification of amenable mutant forms of α -Gal A using the Migalastat Amenability Assay. Notably, there are no specific mutations mentioned at all on the page that Dr. Medin cites or anywhere on the poster.⁴²⁰ In my opinion, the disclosure that the Migalastat Amenability Assay is highly predictive of pharmacodynamic response to oral administration of migalastat does not provide a person of ordinary skill in the art with a motivation to treat any specific Fabry disease patient with

⁴¹⁶ Medin Opening Report, ¶ 198 (quoting Giugliani, Abstract), Ex. C at 16.

⁴¹⁷ Giugliani, Abstract.

⁴¹⁸ See Giugliani, Abstract.

⁴¹⁹ Medin Opening Report, ¶¶ 204, 224 (citing Benjamin 2016 at 7), Ex. C at 14-16.

⁴²⁰ See Benjamin 2016 at 7.

migalastat. In addition, Benjamin 2016 does not disclose treatment of Fabry patients with any of the specific mutations in Claim 9. Thus, it is my opinion that Benjamin 2016 does not provide any teaching on the single α -Gal A mutation, I242F, from Claim 9 of the '490 Patent.

304. Dr. Medin also opines that Benjamin 2016 “discloses the administration of migalastat.”⁴²¹ I disagree. Benjamin 2016 does not have any information of any specific α -Gal A mutations, and which mutations may be amenable to treatment with migalastat. Without this information, a person of ordinary skill in the art would not be motivated to treat Fabry patients generally with migalastat. This is especially the case because Benjamin 2016 confirms that migalastat cannot be used for all Fabry patients, and thus mutation specific treatment is required.⁴²² Thus, it is my opinion that Benjamin 2016 does not provide any teaching on how to treat Fabry patients with the α -Gal A mutations from Claim 9 of the '490 Patent.

305. Dr. Medin opines that “[a] [person of ordinary skill in the art] would have known that HEK-293 cells were first described in the late 1970s and as early as 1992, these cells were used for transfection and analyses of variant proteins and thus would have been a known tool in the toolbox of a [person of ordinary skill in the art].”⁴²³ Although use of a HEK cell-based assay was known, what was not known was how to use such an assay to reliably identify amenable and nonamenable mutations.

306. Dr. Medin opines that “[a]s of the earliest priority date to which the claims of the '490 patent is entitled, the HEK assay amenable mutations of α -galactosidase A recited in at least

⁴²¹ Medin Opening Report, ¶ 198 (citing Benjamin 2016 at 2), Ex. C at 16.

⁴²² See Benjamin 2016, at 2 (“Approximately 30-50% of patients with FD are estimated to have amenable mutations”).

⁴²³ Medin Opening Report, ¶ 203.

claim 1 would have been obvious to a [person of ordinary skill in the art].”⁴²⁴ I disagree. As of the time of the invention of Claim 9 of the ’490 Patent, a person of ordinary skill in the art would have understood that the mutation I242F was non-responsive to migalastat based on the ’319 Patent Publication. Dr. Medin points to no reason why a person of ordinary skill in the art would have believed the opposite is true.

307. Dr. Medin next opines that “[i]t was known that mutations in the GLA gene that encode α -galactosidase A (α -Gal A) cause Fabry disease,” and that “[b]y 2011, more than 600 disease-causing mutations in the GLA gene had been identified . . . and by March 2016, more than 800 disease-causing mutations in the GLA gene had been identified”⁴²⁵ In my opinion, the high number of unique GLA mutations that had been discovered adds to the complexity of the methods of treatment with migalastat and supports the nonobviousness of Claim 9. In my opinion, it would not have been obvious to try treatment with migalastat for Fabry patients with the specific mutations of Claim 9 of the ’490 Patent and, especially given the unpredictability of whether or not Fabry patients with a given mutation would respond to treatment with migalastat; further, a person of ordinary skill in the art would not have had a reasonable expectation of success with respect to treating Fabry patients that carry the mutation of Claim 9 with migalastat.

308. Dr. Medin opines that “[i]t was well known that migalastat selectively binds and stabilizes α -Gal A, and that a HEK-293 cell-based assay could be used to identify mutant forms of α -Gal A that are responsive to migalastat.”⁴²⁶ Dr. Medin further opines that “[t]he prior art further teaches the use of a HEK-293 cell-based assay to identify patients with α -Gal A

⁴²⁴ Medin Opening Report, ¶¶ 208, 228 (same but including Claim 9).

⁴²⁵ Medin Opening Report, ¶¶ 208, 228.

⁴²⁶ Medin Opening Report, ¶¶ 208, 228.

mutations that are amenable to migalastat treatment.”⁴²⁷ In my opinion, Dr. Medin has vastly overstated the state of the field at the time the application leading to the ’490 Patent was filed. In fact, the HEK-293 cell-based assay from the ’319 Patent Publication, Wu, Germain 2012, and Giugliani was found to be unable to accurately identify which patients to treat with migalastat. In addition, Wu, Germain 2012, and Giugliani would discourage a person of skill in the art from treating Fabry patients with the mutation in Claim 9 with migalastat, including because had a person of ordinary skill in the art used the assay discussed in these references to determine whether Fabry patients with the mutation in Claim 9 were responsive to treatment with migalastat, he or she would have found that this mutation is categorized as nonresponsive and therefore would not have been motivated to treat such Fabry patients with migalastat. In addition, Benjamin 2016 did not disclose full information about the Migalastat Amenability Assay, including critical information about which mutations were found amenable or not in that assay. Further, Benjamin 2016 does not disclose treatment of Fabry patients with any of the specific mutations in Claim 9. Indeed, pharmacological chaperones were a relatively new avenue of treatment that was being explored. As of the priority date, there were no FDA approved pharmacological chaperones for any disease, let alone for Fabry disease.⁴²⁸ Although

⁴²⁷ Medin Opening Report, ¶¶ 209, 229.

⁴²⁸ See e.g., Keyzor I., et al., (2023) Therapeutic Role of Pharmacological Chaperones in Lysosomal Storage Disorders: A Review of the Evidence and Informed Approach to Reclassification, *Biomolecules* **13**(8):1227 (“The term “pharmacological chaperone therapy” or “PCT” was first coined in 2000 to describe the category of exogenously administered small molecules that restore folding and trafficking defects of misfolded proteins in LSDs. The EMA approved the first commercially available PCT, migalastat (Galafold®; Amicus Therapeutics Inc., Philadelphia, PA, USA), in 2016, for long-term treatment of adults with Fabry disease who have an amenable mutation (i.e., a mutation that is responsive to treatment).”) (internal citation omitted) (ATGAL_10161626 at -627); May 31, 2016, Amicus Therapeutics Announces European Commission Approval for Galafold™ (Migalastat) in Patients with Fabry Disease in European Union (ATGAL_07336052 at -052); Moran, N., (2018) FDA Approves Galafold, a Triumph for Amicus, *Nat. Biotech.* 36:91 (ATGAL_10161450 at -450).

there were theories about how migalastat may be able to selectively bind and stabilize α -Gal A in certain situations, it was unknown when this would occur and the disclosures in the art at the time suggested that it was highly unpredictable which mutated α -Gal A would be stabilized by migalastat. Further, the HEK assay referred to in those references was determined to be unreliable, including because it was used for enrollment in Amicus's phase 3 clinical studies, which resulted in the 011 study failing to meet its endpoint for the first six months of data.

309. Dr. Medin opines that "it would have been obvious for a [person of ordinary skill in the art] to simply carry out the steps of a known cell and enzyme assay to identify the naturally-occurring α -galactosidase A mutations recited in at least claim 9."⁴²⁹ For all of the reasons discussed above, I disagree. Further, as I discussed above, the mutation of Claim 9, I242F, was identified as non-responsive to migalastat.⁴³⁰ As such, a person of ordinary skill in the art would have no reason to re-test this mutation based on these prior art references or any guidance as to how to re-test this mutation in a different assay. Further, Dr. Medin points to no reason why a person of ordinary skill in the art would have found this particular mutation and been motivated to re-test these mutations to treat patients with one of those mutations, much less how the mutations may be re-tested, or any reason why a person of ordinary skill in the art would have had a reasonable expectation of success in doing so.

310. Dr. Medin also opines that "[a] [person of ordinary skill in the art] seeking to improve upon the existing treatments of Fabry disease would have been motivated with a reasonable expectation of success to combine the disclosures of Wu, and/or Germain 2012, in view of Benjamin (2016) and/or Giugliani, and the knowledge of a [person of ordinary skill in

⁴²⁹ Medin Opening Report, ¶¶ 229, 209.

⁴³⁰ See '319 Patent Publication at Figs.17, 18.

the art].”⁴³¹ He also opines that “a [person of ordinary skill in the art] would have been motivated to combine the teachings of Wu, Germain 2012, Giugliani, and/or Benjamin (2016) because they all have complementary teachings and show consistent outcomes, therefore, a [person of ordinary skill in the art] would also have an expectation of success in doing so.”⁴³² I also disagree with these opinions. Dr. Medin fails to explain exactly which disclosures of Wu, Germain 2012, Benjamin 2016, and Giugliani a person of ordinary skill in the art would combine and why there is a motivation to combine, and why doing so would result in a reasonable expectation of success. Simply saying they have “complementary teachings and show consistent outcomes” does nothing to explain why there would be a reasonable expectation of success. Further, although Dr. Medin mentions knowledge of a person of ordinary skill in the art, he fails to identify what that knowledge is.

311. Dr. Medin opines that “Wu discloses ‘the administration of ‘a dose of 150 mg [migalastat hydrochloride] every other day’ as a potential treatment for Fabry disease.”⁴³³ Dr. Medin further opines that Wu “discloses ‘the administration of different [migalastat hydrochloride] doses (50, 150, or 250 mg).’”⁴³⁴ Dr. Medin overstates what Wu discloses. Wu actually discloses that:

The degree of consistency found in the current comparison of HEK-293 cell-based and in vivo mutant α -GAL A responses does not necessarily indicate the degree of consistency that would be seen with any particular dose or regimen of [migalastat hydrochloride]. This is because the in vivo α -GAL A responses analyzed here were obtained following different [migalastat hydrochloride]

⁴³¹ Medin Opening Report, ¶ 210; *see also* Medin Opening Report, ¶¶ 211, 230.

⁴³² Medin Opening Report, ¶¶ 212, 231.

⁴³³ Medin Opening Report, ¶ 216 (citing Wu at 974).

⁴³⁴ Medin Opening Report, ¶ 216.

doses (50, 150, or 250 mg) and with various regimens (every other day, twice per day, or every day), according to the different clinical study protocols.⁴³⁵

In my opinion, this is a disclosure of specific doses and dose regimens provided to a limited number of specific Fabry patients with specific mutations. It does not disclose that any such dosages or regimens could be used to treat Fabry patients with other α -Gal A mutations or that a specific dose or regimen is recommended for Fabry patients with the mutation in Claim 9.

312. Dr. Medin opines that Germain 2012 discloses “oral administration of 150 mg migalastat HCl every other day.”⁴³⁶ Dr. Medin again overstates this disclosure because like Wu, Germain 2012 relates to treatment of a limited number of specific Fabry patients with specific Fabry mutations at specific doses and dose regimens. It does not disclose that a specific dose or regimen is recommended for Fabry patients with the mutation in Claim 9.

313. Dr. Medin opines that Giuliani discloses “the oral administration of migalastat hydrochloride at doses of 50 mg, 150 mg, and 250 mg every other day (QOD) to females with Fabry disease.”⁴³⁷ Dr. Medin again overstates this disclosure because like Wu and Germain 2012, Giuliani relates to treatment of a limited number of specific Fabry patients with specific Fabry mutations at specific doses and dose regimens. It does not disclose that a specific dose or regimen is recommended for Fabry patients with the mutation in Claim 9.

314. Dr. Medin opines that Benjamin 2016 discloses “administration of 150 mg migalastat HCl.”⁴³⁸ Dr. Medin’s reliance on Benjamin 2016 is also misplaced because Benjamin 2016 does not disclose treatment of Fabry patients with the I242F mutation in Claim 9 of the

⁴³⁵ Wu at 975.

⁴³⁶ Medin Opening Report, ¶ 216 (citing Germain 2012 at Abstract), Ex. C at 16.

⁴³⁷ Medin Opening Report, ¶ 216 (citing Giuliani at Abstract), Ex. C at 16.

⁴³⁸ Medin Opening Report, ¶ 216 (citing Benjamin at 4), Ex. C at 16.

'490 Patent, nor does it disclose use of 150 mg every other day with respect to this mutation. In fact, Benjamin 2016 does not identify any amenable mutation based on the Migalastat Amenability Assay.

315. Dr. Medin opines that “a [person of ordinary skill in the art] would have been motivated to combine the teachings of Wu, Germain 2012, Giugliani, and/or Benjamin (2016) for this dosing because they all have complementary teachings and show consistent outcomes, therefore, a [person of ordinary skill in the art] would also have an expectation of success in doing so.”⁴³⁹ I disagree. Dr. Medin fails to explain exactly which disclosures of Wu, Germain 2012, Benjamin 2016, and Giugliani a person of ordinary skill in the art would combine and why there is a motivation to combine, and why doing so would result in a reasonable expectation of success. Simply saying they have “complementary teachings and show consistent outcomes” does nothing to explain why there would be a reasonable expectation of success. Further, although Dr. Medin mentions knowledge of a person of ordinary skill in the art, he fails to identify what that knowledge is.

316. Dr. Medin opines that “[a] [person of ordinary skill in the art] would have been motivated to combine the teachings of Wu, Germain 2012, Benjamin (2016), and Giugliani, in view of the knowledge of a [person of ordinary skill in the art], at least because each is directed to guiding the use of migalastat in the treatment of Fabry disease and/or the evaluation of mutations in the α -galactosidase A gene in patients with Fabry disease in order to guide treatment options for Fabry disease, including treatment with migalastat.”⁴⁴⁰ I disagree. In my opinion, a person of ordinary skill in the art would not have combined results or teachings from

⁴³⁹ Medin Opening Report, ¶ 217, Ex. C at 15-18.

⁴⁴⁰ Medin Opening Report, ¶ 210, Ex. C at 15-18; *see also* Medin Opening Report, ¶¶ 211, 230.

Benjamin 2016 with those of Wu, Germain 2012, and Giugliani to treat Fabry patients with the mutation of Claim 9 of the '490 Patent because they would have no reason to do it. More importantly, even if a person of ordinary skill in the art did combine such references, such person of ordinary skill in the art would not be motivated to reach the invention claimed in Claim 9 with any reasonable expectation of success for all of the reasons described above, including, e.g., because the I242F mutation in Claim 9 is not disclosed in these references as being amenable to migalastat.

317. It is unclear what combination Dr. Medin is even relying upon for his analysis of Claim 9. Because Dr. Medin's obviousness combinations are unclear, I reserve the right to supplement my opinions based on any additional and/or clarifying opinions that Dr. Medin renders with respect to Claim 9. Further, Dr. Medin fails to identify what he is using as his base reference, how he is modifying it and what reference he is modifying it with, and why a person of ordinary skill in the art would have been motivated to modify the reference or have had a reasonable expectation of success in such a combination. Dr. Medin more generally fails to explain how he is combining the prior art references and why, in his opinion, such references would cause a person of ordinary skill in the art to reach the claimed invention. In addition, he generally fails to acknowledge the fact that the prior art references he relies on do not disclose treating Fabry patients with the specific mutation in Claim 9 and he fails to explain how a person of ordinary skill in the art would reach such a method of treatment for those specific mutations based on the references he relies upon.

318. Dr. Medin opines that "claim 7 would have been obvious to a [person of ordinary skill in the art] over Wu and/or Germain 2012 in view of Benjamin (2016), and/or Giugliani, and

the knowledge of a [person of ordinary skill in the art].”⁴⁴¹ As stated above, I understand Claim 7 is not asserted, and I have been asked to respond only as to Claim 9. To the extent Dr. Medin intends to refer to asserted Claim 9, for all the reasons discussed herein, in my opinion, Dr. Medin has failed to prove that Claim 9 is obvious. Based on my review of the prior art references and the disclosures cited, in my opinion, Claim 9 is not obvious and there is no motivation to combine the references with any reasonable expectation of success in reaching the invention of Claim 9. Dr. Medin generally fails to acknowledge the fact that the prior art references he relies on do not disclose treating Fabry patients with the specific mutations in Claim 9 and he fails to explain how a person of ordinary skill in the art would reach such a method of treatment for those specific mutations based on the references he relies upon, why a person of ordinary skill in the art would combine them, and why such a person would have a reasonable expectation of success in doing so.

F. Claims 23-27 of the '164 Patent

319. As an initial matter, it is unclear to me what combination of references Dr. Medin is using for his prior art combinations for Claims 23-27 of the '164 Patent. Dr. Medin opines in the summary of his opinions that:

[b]y way of example, the asserted claims are rendered obvious by the following combinations:

- 1) The '319 patent publication in view of Lockhart 093 and the knowledge of a [person of ordinary skill in the art]
- 2) Wu, Germain [2012], Benjamin [2016], and/or Giugliani and the knowledge of a [person of ordinary skill in the art]

⁴⁴¹ Medin Opening Report, ¶ 216.

- 3) Wu and/or Germain [2012] in view of Benjamin [2016] and/or Giuliani and the knowledge of a [person of ordinary skill in the art.]⁴⁴²

Dr. Medin seems to imply that there could be additional combinations, but he does not explicitly disclose what those additional combinations might be. Accordingly, I will respond to the opinions and specific combinations that Dr. Medin actually analyzed in his report, and I reserve the right to respond to any additional combinations should Dr. Medin later render an opinion as to such combinations.

320. Moreover, this list results in dozens of possible combinations of prior art references. Dr. Medin does not actually analyze each of these combinations in his report. Thus it is unclear what teaching(s) Dr. Medin proposes to take from each reference and why a person of ordinary skill in the art would have been motivated to combine those elements or teachings with a reasonable expectation of success. Instead, Dr. Medin's only obviousness analysis is him analyzing six references, the '319 Patent Publication, Lockhart '093, Wu, Germain 2012, Benjamin 2016, and Giuliani individually without specifying how to combine them within the context of his proposed obviousness combinations let alone why a person of ordinary skill in the art would be motivated to combine those references in such a way. For example, Dr. Medin fails to explain what reference he is starting with and how he is modifying such reference with the other prior art references.⁴⁴³ Accordingly, I will respond to the opinions that Dr. Medin actually included in his report regarding the disclosed combinations, and I reserve the right to respond to any additional opinions about those combinations should Dr. Medin later render any opinion

⁴⁴² Medin Opening Report, ¶ 13.

⁴⁴³ *See generally* Medin Opening Report, § IX.E (element by element analysis of the asserted claim of the '164 patent); *see also* Medin Opening Report, Exhibit C (claim chart including list of citations to each of the six asserted prior art references without separating by combination).

about what and how the specific references are to be combined and/or the motivation to combine or modify such specific references.

321. Based on my review of Dr. Medin's report, he fails to provide his combinations or overall conclusion as to whether or not the claim is obvious for many of the asserted claims of the '164 Patent.

1. Claim 23

322. Claim 23 of the '164 Patent (bolded below) is an independent claim and recites:

23. A method for treatment of Fabry disease in a human patient in need thereof, the method comprising orally administering to the patient about 123 mg free base equivalent of migalastat or a salt thereof every other day, wherein the patient has an α -galactosidase A mutation selected from the group consisting of: Y184S, N228H, or T412I.

323. Based on my review of Dr. Medin's report, it is unclear what combinations Dr. Medin asserts for Claim 23. Dr. Medin lists only the following combinations in the summary of his opinions:

- 1) The '319 patent publication in view of Lockhart '093 and the knowledge of a person of ordinary skill in the art;
- 2) Wu, Germain [2012], Benjamin 2016, and/or Giugliani and the knowledge of a person of ordinary skill in the art;
- 3) Wu and/or Germain [2012] in view of Benjamin 2016 and/or Giugliani and the knowledge of a person of ordinary skill in the art.⁴⁴⁴

324. Regarding the first combination—Dr. Medin did not identify what knowledge a person of ordinary skill in the art would have had that is relevant to this combination or why a person of ordinary skill in the art would have been motivated to use that knowledge to modify what is disclosed in the '319 Patent Publication.

⁴⁴⁴ Medin Opening Report, ¶ 13.

325. Regarding the second combination—Wu, Germain 2012, Benjamin, and/or Giugliani, and the knowledge of a person of ordinary skill in the art—it is unclear exactly which of those references he is combining and how those references are being combined. Dr. Medin discusses each of the four references individually before alleging in a conclusory fashion that they could be combined with no explanation of how they would be combined.⁴⁴⁵ Dr. Medin again failed to identify what knowledge a person of ordinary skill in the art would have had that is relevant to this combination or why a person of ordinary skill in the art would have been motivated to use that knowledge to modify what is disclosed in the references cited by Dr. Medin.

326. Regarding the third combination—Wu and/or Germain 2012 in view of Benjamin 2016 and/or Giugliani and the knowledge of a person of ordinary skill in the art—it is unclear exactly which of those references he is combining and how those references are being combined. Like with the second combination, Dr. Medin discusses each of the four references individually before alleging in a conclusory fashion that they would be combined, with no explanation of how they would be combined or why a person of ordinary skill in the art would combine them.⁴⁴⁶

⁴⁴⁵ See Medin Opening Report, ¶ 252 (“In addition, a POSA [person of ordinary skill in the art] would have been motivated to combine the teachings of Wu, Germain [2012], Giugliani and/or Benjamin (2016) because they all have complementary teachings and show consistent outcomes, therefore, a POSA [person of ordinary skill in the art] would also have an expectation of success in doing so.”); *see also* Medin Opening Report, ¶ 251 (“A POSA [person of ordinary skill in the art] would have been motivated with a reasonable expectation of success to combine the teachings of Wu, Germain 2012, Benjamin (2016), and/or Giugliani, at least because each is directed to the use of migalastat in the treatment of Fabry disease and/or the evaluation of mutations in the α -galactosidase A gene in patients with Fabry disease that inform treatment options for Fabry disease, including treatment with migalastat.”); *see also* Medin Opening Report, ¶¶ 268-269 (for Claim 25), ¶¶ 279-280 (for Claim 26); ¶¶ 290-291 (for Claim 27).

⁴⁴⁶ See Medin Opening Report, ¶ 251 (“Furthermore, a POSA [person of ordinary skill in the art] seeking to improve upon the existing treatments of Fabry disease would have been motivated with a reasonable expectation of success to combine the disclosures of Wu, and/or Germain 2012

Again, Dr. Medin failed to identify what knowledge a person of ordinary skill in the art would have had that is relevant to this combination or why a person of ordinary skill in the art would have been motivated to use that knowledge to modify what is disclosed in the references cited by Dr. Medin.

327. In my opinion, as discussed further below, Dr. Medin's combinations do not disclose the limitations of Claim 23 and do not render Claim 23 obvious.

a) Asserted Combination 1: the '319 Patent Publication in view of Lockhart '093 and the Knowledge of a Person of Ordinary Skill in the Art

328. To support his obviousness opinions, Dr. Medin cites to Proposed Claim 10 of the '319 Patent Publication to argue that methods for treating Fabry with migalastat was known.⁴⁴⁷ I disagree. The '319 Patent Publication discloses results of an in vitro HEK assay with respect to specific mutations and that some, but not all, mutations are responsive to migalastat. It does not teach a general method of treatment for Fabry disease by administering migalastat to any Fabry patient.

329. Dr. Medin relies on Proposed Claim 10 of the '319 Patent Publication, which states:

10. A method of treating a patient diagnosed with Fabry disease which comprises administering to the patient a therapeutically effective dose of 1-deoxygalactonorjirimycin, wherein the patient expresses a mutant α -galactosidase A selected from the group consisting of the α -galactosidase A mutations A257D, A257G, A257P, A291T, A292T, A307T, A309P, A352V, A368T, A73V, A97V, C174G, C174R, C56F, C56Y, D165H, D313G, D322E, D55V, E203V, F169S, G171R, G183A, G183V, G258R, G258V, G261D, G325S, G360D, G360S, G85D, G85M, I117S, I198T, I239T, I253T, I289S, I319T, I359T, K185E, K308N, L166G, L16H, L19P, L243W, L36F, L36S,

in view of Benjamin (2016) and/or Giuliani, and the knowledge of a POSA [person of ordinary skill in the art]."); *see also* Medin Opening Report, ¶ 268 (for Claim 25), ¶ 279 (for Claim 26); ¶ 290 (for Claim 27).

⁴⁴⁷ Medin Opening Report, ¶ 233, Ex. C at 19; *see also* Medin Opening Report, ¶¶ 261, 272, 283.

L372P, L403S, L54P, M290I, M290L, M296L, M296T, M42L, M42R, M76T, M96I, N53L, P205S, P293T, P409A, P409T, P60L, Q107L, Q250P, Q312R, Q321H, Q321L, R301G, R356G, S238N, S247C, T282A, T410I, V339E, W162G, W349S, Y152C, Y184C, Y200C, Y207H and Y216C.⁴⁴⁸

Proposed Claim 10 of the '319 Patent Publication does not include any of the specific α -Gal A mutations in Claim 23 of the '164 Patent.

330. Dr. Medin also opines that the '319 Patent Publication “discloses that the mutations A20P, I242N, A309P, A352V, R356G, and R356W are responsive to migalastat, i.e., they are HEK assay amenable mutations.”⁴⁴⁹ Dr. Medin then opines that “a [person of ordinary skill in the art] would know that amino acid positions 20, 242, 309, 352, and 356 on α -galactosidase A have missense mutations in Fabry patients and would therefore be motivated to explore other mutations at the same amino acid positions.”⁴⁵⁰

331. As a preliminary matter, Dr. Medin seems to be mixing up the concepts of responsiveness in the HEK assay described in the '319 Patent Publication with the concept of HEK assay amenable mutations described in the '164 Patent. In drawing this inappropriate parallel, Dr. Medin is using the '164 Patent's disclosures and thus is using hindsight to support his obviousness arguments. The assay in the '319 Patent Publication is different than the assay in the '164 Patent.

332. Further, I disagree with Dr. Medin's opinions for several other reasons. *First*, as described above in the technology background (§VI), Fabry disease is difficult to diagnose and treat because there are many different α -Gal A mutations that cause Fabry disease. Each

⁴⁴⁸ '319 Patent Publication, Proposed Claim 10.

⁴⁴⁹ Medin Opening Report, ¶ 241, Ex. C at 20 & 22-24; *see also* Medin Opening Report, ¶¶ 261, 272, 283 (arguing the same for claims 25, 26, 27).

⁴⁵⁰ Medin Opening Report, ¶ 241; *see also* Medin Opening Report, ¶¶ 261, 272, 283 (arguing the same for claims 25, 26, 27).

mutation may cause different symptoms, ultimately causing different presentations of the disease in each patient. A disclosure that a patient with one of the α -Gal A mutations, for example, as in Proposed Claim 10 of the '319 Patent Publication, could be treated with migalastat does not inform a person of ordinary skill in the art whether other Fabry disease patients with different α -Gal A mutations could be treated with migalastat. Further, the '319 Patent Publication discloses examples of an α -Gal A mutation at a specific amino acid location being responsive to treatment with migalastat and a different mutation at the same location is not.⁴⁵¹ In fact, the '319 Patent Publication itself recognizes that there is no way to predict with a Fabry patient with a specific mutation will be responsive or not to treatment with migalastat prior to testing.⁴⁵² This remains true even if the mutation occurs at the same position in the α -Gal A protein. For example, the '319 Patent Publication discloses that the L16H, N34K, R112H, N224S, A352V mutations are responsive to treatment with migalastat but the L16P, N34S, R112C, R112S, N224D, A352P, A352D mutations are non-responsive to treatment with migalastat.⁴⁵³ Thus, a person of ordinary skill in the art would not be motivated based on the disclosures of the '319 Patent Publication to look for other α -Gal A mutations at the same amino acid position as a mutation that is reported as responsive to treatment with migalastat in the '319 Patent Publication. The '319 Patent Publication, including Proposed Claim 10, does not include any of the α -Gal A mutations in

⁴⁵¹ '319 Patent Publication, at Fig. 17 (showing responsive GLA mutations L16H, N34K, R112H, N224S, A352V); '319 Patent Publication, Fig. 18 (showing non-responsive GLA mutations L16P, N34S, R112C, R112S, N224D, A352P, A352D).

⁴⁵² See, e.g., '319 Patent Publication, ¶ 0150 ("DGJ-responsive and non-responsive mutant forms did not appear to be located to particular regions or domains on the α -Gal A protein structure."); '319 Patent Publication, ¶ 0146 ("No significant correlation between response and location on the protein sequence of a mutation was observed, suggesting that responsive as well as non-responsive mutations are distributed widely across the entire protein.").

⁴⁵³ See '319 Patent Publication, at Figs. 17–18.

Claim 23 of the '164 Patent and therefore does not disclose or render obvious treatment of Fabry patients with the specific α -Gal A mutations of Claim 23 with migalastat. Just because a specific mutation at a particular amino acid position results in an α -Gal A protein that is responsive to treatment with migalastat as measured by the HEK assay discussed in the '319 Patent Publication does not allow a person of ordinary skill in the art to predict which other mutations at the same amino acid position may be responsive.

333. **Second**, none of the A20P, I242N, A309P, A352V, R356G, and R356W mutations are included in Claim 23 of the '164 Patent. There is no other reason Dr. Medin points to that would lead a person of ordinary skill in the art to treat Fabry patients with one of the specific mutations in Claim 23 with migalastat based on the disclosure in the '319 Patent Publication that different mutations are responsive to treatment with migalastat. In addition, none of the mutations in Claim 23 of the '164 Patent are at any of these amino acid positions.

334. **Third**, the '319 Patent Publication discloses that some α -Gal A mutations are responsive to treatment with migalastat and some are not.⁴⁵⁴ In addition, the '319 Patent Publication references hundreds of missense mutations and there are many different positions for possible mutations. Dr. Medin cherry picks these amino acid positions for a select few of the hundreds of mutations based on hindsight. Dr. Medin presents no reason why a person of ordinary skill in the art would look to these few mutations rather than the hundreds of others in the '319 Patent Publication.

335. Further, Dr. Medin also opines that the '319 Patent Publication “discloses that the α -galactosidase A mutation D322N was generated by site-directed mutagenesis” and that “ α -galactosidase A mutations A13P, Q57L, P146S, and I242F were generated by site-directed

⁴⁵⁴ See, e.g., '319 Patent Publication, at Figs. 17–18.

mutagenesis.”⁴⁵⁵ These mutations are not in Claim 23 of the ’164 Patent, so it is unclear why Dr. Medin points to them here. Dr. Medin opines that “[t]he specification of the ’489 [sic] Patent identifies these mutations as HEK assay amenable mutations.”⁴⁵⁶ In my opinion, Dr. Medin is using hindsight, and the teachings of the ’164 Patent, for his obviousness analysis with respect to Claim 23 of the ’164 Patent.

336. Dr. Medin further opines that “[a]s being HEK assay amenable is an inherent property of the identified mutations, this claim limitation would have inherently existed in the prior art.”⁴⁵⁷ It is not clear to me what Dr. Medin is suggesting and Dr. Medin ignores that none of the mutations he points to are in Claim 23 and none of the mutations in Claim 23 are in the ’319 Patent Publication.

337. Dr. Medin opines that “[a] [person of ordinary skill in the art] would have been motivated to identify patients with GLA mutations suffering from Fabry disease, also determining if these mutations are HEK assay amenable mutations, and once a mutation was, for example, determined to be an HEK assay amenable mutation, to administer migalastat to patients having these mutations.”⁴⁵⁸ I disagree with this opinion. For example, with respect to the specific mutations in Claim 23, a person of ordinary skill in the art would not have known to look for such mutations because it had not yet been discovered in Fabry patients as of the priority date. Further, there were an untold number of mutations that had not yet been discovered (there

⁴⁵⁵ Medin Opening Report, ¶ 242 (citing ’319 Patent Publication, Fig. 1A); *see also* Medin Opening Report, ¶ 262 (claim 25), ¶ 273 (claim 26), ¶ 284 (claim 27).

⁴⁵⁶ Medin Opening Report, ¶ 242; *see also* Medin Opening Report, ¶ 262 (claim 25), ¶ 273 (claim 26), ¶ 284 (claim 27).

⁴⁵⁷ Medin Opening Report, ¶ 242; *see also* Medin Opening Report, ¶ 262 (claim 25), ¶ 273 (claim 26), ¶ 284 (claim 27).

⁴⁵⁸ Medin Opening Report, ¶¶ 243, Ex. C at 20-24; *see also* Medin Opening Report, ¶ 263 (claim 25), ¶ 274 (claim 26), ¶ 285 (claim 27).

are nearly countless possible mutations to the α -Gal A enzyme) and Dr. Medin provides no reason why a person of ordinary skill in the art would have looked for Fabry patients with the three mutations in Claim 23 in particular over any other mutation to α -Gal A, much less how the mutations may be re-tested. In addition, the '319 Patent Publication discusses a HEK assay that was found to be unreliable in identifying Fabry patients who could benefit from treatment with migalastat. The inability of the assay discussed in the '319 Patent Publication to accurately predict whether a mutation was responsive or non-responsive to migalastat was demonstrated by the failure to reach the primary endpoint in the six-month data for Amicus's phase 3 clinical trial, which used this assay for enrollment.

338. Dr. Medin opines that “[t]he dosage form described in the '319 Patent Publication is orally administering.”⁴⁵⁹ But Dr. Medin fails to acknowledge that the '319 Patent Publication does not teach oral administration of migalastat or a salt thereof for treatment of Fabry disease in patients with the mutations in Claim 23.

339. Dr. Medin opines that “[i]n Lockhart '093 Example 6, some patients received 150 mg of migalastat every other day for 12 or 24 weeks, while other patients were randomized to receive 50 mg, 150, or 250 mg of migalastat hydrochloride every other day for 12 weeks.”⁴⁶⁰ In my opinion, Dr. Medin overstates the disclosures in Lockhart '093. Lockhart '093 does not disclose that a dose of 150 mg every other day will work for all α -Gal A mutations or even for all amenable mutations. Further, Lockhart '093 does not disclose that 150 mg every other day is an effective dose for Fabry patients with any of the mutations in Claim 23.

⁴⁵⁹ Medin Opening Report, ¶ 236.

⁴⁶⁰ Medin Opening Report, ¶ 236, Ex. C at 19.

340. Dr. Medin opines that “[a]rriving at 123 mg free base equivalent of migalastat or a salt thereof for every other day dosing would be a matter of routine experimentation for a [person of ordinary skill in the art].”⁴⁶¹ Dr. Medin provides no support for this opinion.

341. Dr. Medin then opines that “[a] [person of ordinary skill in the art] would have been aware of the 150 mg every other day dosing of migalastat to treat Fabry Disease and its effectiveness from at least Lockhart ’093, and therefore would have been motivated to rely on this teaching to arrive at the 123 mg free base equivalent every other day dosing.”⁴⁶² Dr. Medin also opines that “[a] [person of ordinary skill in the art] would further have had an expectation of success with this dosing given the teachings of Lockhart ’093.”⁴⁶³ I disagree with these opinions. Lockhart ’093 does not disclose that 123 mg free base equivalent every other day is an effective dose for all Fabry patients or for all Fabry patients with an amenable mutation. Nor does Lockhart ’093 even suggest that 123 mg free base equivalent every other day is the preferred dose and dose regimen of migalastat hydrochloride for any Fabry patient. Lockhart ’093 relies on theoretical dosing models and preliminary data for enrollment of phase 2 studies related to migalastat hydrochloride where a number of different doses and dose regimens were used.⁴⁶⁴ A person of ordinary skill in the art would have understood Lockhart ’093 to be a preliminary investigation into dosing of pharmacological chaperones like migalastat hydrochloride and not some definitive reference of the proper dose of migalastat hydrochloride for all Fabry patients, as Dr. Medin suggests.

⁴⁶¹ Medin Opening Report, ¶ 236.

⁴⁶² Medin Opening Report, ¶ 237, Ex. C at 19.

⁴⁶³ Medin Opening Report, ¶ 237, Ex. C at 19.

⁴⁶⁴ See Lockhart ’093, Exs. 4-6.

342. Dr. Medin makes no conclusions as to whether or not Claim 23 is obvious over any combination and fails to even say what his alleged combination is. For all the reasons discussed herein, in my opinion, Dr. Medin has failed to prove that Claim 23 is obvious. Based on my review of the prior art references and the disclosures cited, in my opinion, Claim 23 is not obvious and there is no motivation to combine the references with any reasonable expectation of success in reaching the invention of Claim 23. Dr. Medin generally fails to acknowledge the fact that the prior art references he relies on do not disclose treating Fabry patients with the specific mutations in Claim 23 and he fails to explain how a person of ordinary skill in the art would reach such a method of treatment for those specific mutations based on the references he relies upon, why a person of ordinary skill in the art would combine them, and why such a person would have a reasonable expectation of success in doing so.

b) Asserted Combination 2: Undisclosed Combination of Wu, Germain 2012, Giugliani, and/or Benjamin 2016 and the Knowledge of a Person of Ordinary Skill in the Art;

and

Asserted Combination 3: Wu and/or Germain 2012 in View of Benjamin 2016 and/or Giugliani and the Knowledge of a Person of Ordinary Skill in the Art

343. For the vague combination of Wu, Germain 2012, Giugliani, and Benjamin 2016, Dr. Medin just cherry picks what each reference discloses about migalastat and its administration. Dr. Medin, however, does not discuss how these specific disclosures render this claim element obvious. For example, according to Dr. Medin, Wu discloses that “migalastat hydrochloride (AT1001, GR181413A) [is] currently in clinical development to evaluate its safety

and efficacy as a potential treatment for Fabry disease”⁴⁶⁵ and that “AT1001 (migalastat hydrochloride, 1-deoxygalactonojirimycin) is a pharmacological chaperone for α -Gal A that is in Phase 3 clinical development as a potential therapy for Fabry disease.”⁴⁶⁶ If Dr. Medin is arguing that these disclosures render Claim 23 obvious, I disagree. Dr. Medin overreads Wu. Wu’s teachings are directed to a certain subset of Fabry patients rather than all Fabry patients, and certainly not all Fabry patients with amenable mutations. For example, Wu states that “a pharmacological chaperone may be a viable treatment for Fabry disease, serving as an alternative to enzyme replacement therapy *for some patients*.”⁴⁶⁷ Wu also recognizes that not all Fabry patients benefit from treatment with migalastat.⁴⁶⁸ Wu also discloses that “[f]urther evaluation of the utility of the HEK-293 cell-based assay for Fabry patient selection for treatment with AT1001 [migalastat hydrochloride] is ongoing.”⁴⁶⁹ In my opinion, a person of ordinary skill in the art would understand this disclosure to mean that Wu is limited to specific Fabry patients in certain Amicus’s phase 2 clinical trials.⁴⁷⁰ In addition, although Wu mentions Phase 3 clinical trials, it does not disclose what mutations are being studied in those trials, or whether any such mutations can be treated with migalastat. Further, a skilled artisan would have understood that the initial data from those phase 3 clinical studies was reported by Amicus as “not meet[ing]

⁴⁶⁵ Medin Opening Report, ¶ 234 (quoting Wu at 965, 974), Ex. C at 19-24; *see also* Medin Opening Report ¶ 266 (claim 25); ¶ 277 (claim 26); ¶ 288 (claim 27).

⁴⁶⁶ Medin Opening Report, ¶ 234 (quoting Wu at 965, 974), Ex. C at 19-24.

⁴⁶⁷ Wu at 965 (emphasis added).

⁴⁶⁸ Wu at 975.

⁴⁶⁹ Wu at 976.

⁴⁷⁰ Wu at Table 2 (discussing FAB-CL-201, FAB-CL-202, and FAB-CL-203 trial data).

statistical significance.”⁴⁷¹ As such, Wu does not provide reliable methods of treating Fabry patients, even for the mutations explicitly discussed in the reference, and the disclosures cannot be used to extrapolate any methods of treatment for Fabry patients who are not discussed in the reference. Thus, it is my opinion that Wu does not provide any teaching on how to treat Fabry patients with the specific α -Gal A mutations from Claim 23 of the ’164 Patent.

344. Next, Dr. Medin quotes Germain 2012’s disclosure that “[m]igalastat HCl is a candidate pharmacological chaperone that provides a novel genotype-specific treatment for [Fabry disease].”⁴⁷² Again, Dr. Medin does not discuss how this specific disclosure renders Claim 23 of the ’164 Patent obvious. Even this disclosure recognizes that the treatment would be “genotype-specific” and thus cannot be applied to all Fabry patients. This is because Germain 2012 discloses results from only a limited number of Fabry patients with specific mutations, none of which overlap with those in Claim 23 of the ’164 Patent.⁴⁷³ As such, a person of ordinary skill in the art would understand that certain patients would not benefit from treatment with migalastat hydrochloride. Absent specific disclosure that a patient with a specific mutation would benefit from migalastat treatment, a skilled artisan would not be motivated to treat such patients with migalastat. Thus, it is my opinion that Germain 2012 does not provide any teaching on how to treat Fabry patients with the disclosed GLA mutations from Claim 23 of the ’164 Patent.

⁴⁷¹ Amicus Website, Press Release dated Feb. 15, 2013, available at <https://ir.amicusrx.com/news-releases/news-release-details/amicus-therapeutics-presents-additional-6-month-results-phase-3>.

⁴⁷² Medin Opening Report, ¶ 234 (quoting Germain 2012, Abstract), Ex. C at 19-24.

⁴⁷³ See Germain 2012 at Abstract (describing results from two phase 2 studies of nine males with Fabry disease).

345. Dr. Medin quotes Giugliani's disclosure of the "evaluation of 'the safety and pharmacodynamics of migalastat hydrochloride, an investigational pharmacological chaperone given orally every other day (QOD) to females with FD.'" ⁴⁷⁴ Again, Dr. Medin does not discuss how this specific disclosure renders Claim 23 of the '164 Patent obvious. Giugliani discloses specific results related to "nine females with [Fabry disease]." Giugliani, Abstract. As such, a person of ordinary skill in the art would not understand such disclosure could be extracted to all Fabry disease patients, regardless of their specific α -Gal A mutation. ⁴⁷⁵ Thus, it is my opinion that Giugliani does not provide any teaching on how to treat Fabry patients with the α -Gal A mutations from Claim 23 of the '164 Patent.

346. Lastly, Dr. Medin states that Benjamin 2016 "discloses orally administered migalastat for treating Fabry Disease patients as an investigational pharmacological chaperone for patients with amenable mutations." ⁴⁷⁶ Again, Dr. Medin does not discuss how this specific disclosure renders Claim 23 of the '164 Patent obvious. Benjamin 2016 does not have any information of any specific α -Gal A mutations, and which mutations may be amenable to treatment with migalastat. Without this information, a person of ordinary skill in the art would not be motivated to treat Fabry patients generally with migalastat. This is especially the case because Benjamin 2016 confirms that migalastat cannot be used for all Fabry patients, and thus mutation specific treatment is required. ⁴⁷⁷ Thus, it is my opinion that Benjamin 2016 does not

⁴⁷⁴ Medin Opening Report, ¶ 234 (quoting Giugliani, Abstract), Ex. C at 19-24.

⁴⁷⁵ See Giugliani, Abstract.

⁴⁷⁶ Medin Opening Report, ¶ 234 (citing Benjamin 2016 at 1), Ex. C at 19-24.

⁴⁷⁷ See Benjamin 2016, at 2 ("[Approximately] 30-50% of patients with FD are estimated to have amenable mutations").

provide any teaching on how to treat Fabry patients with the α -Gal A mutations from Claim 23 of the '164 Patent.

347. Dr. Medin opines that “it was well known that a HEK-293 cell-based assay could be used to identify mutant forms of α -GAL A that are responsive to migalastat” and points to disclosures in Germain 2012, Wu, Benjamin 2016, and Giugliani.⁴⁷⁸ In my opinion, this is not an accurate description of the state of the field at the time of the invention of Claim 23 of the '164 Patent with respect to the mutations in the claim, which had not yet been discovered in patients as of the '164 Patent's priority date.

348. In addition, Wu, Germain 2012, and Giugliani disclose a research-based HEK assay. Benjamin 2016 on the other hand discusses the development of another HEK assay. Dr. Medin is conflating these two distinct assays in his analysis. The HEK-293 cell-based assay used in Germain 2012, Wu, and Giugliani could not accurately predict whether a mutation was responsive or non-responsive to migalastat and the disclosures in Benjamin 2016 do not identify to a person of ordinary skill in the art which mutations are being discussed with respect to the Migalastat Amenability Assay and there was no data related to the mutations in Claim 23 as of the priority date of the '164 Patent. The inability of the assay discussed in Germain 2012, Wu, and Giugliani to accurately predict whether a mutation was responsive or non-responsive to migalastat was demonstrated by the failure to reach the primary endpoint in the six-month data for Amicus's phase 3 clinical trial, which used this assay for enrollment.

349. Dr. Medin opines that “[a] [person of ordinary skill in the art] would have known that HEK-293 cells were first described in the late 1970s and as early as 1992, these cells were

⁴⁷⁸ Medin Opening Report, ¶¶ 244-245; *see also* Medin Opening Report ¶¶ 264-65 (claim 25); ¶¶ 275-76 (claim 26); ¶¶ 286-87 (claim 27).

used for transfection and analyses of variant proteins, and thus would have been a known tool in the toolbox of a [person of ordinary skill in the art].”⁴⁷⁹ Dr. Medin is oversimplifying the issue and ignores that the mutations in Claim 23 were not discovered in Fabry patients as of the priority date. It was not routine to use a HEK assay to determine amenability for Fabry patients with mutations that had not yet been discovered.

350. Dr. Medin cites Giuliani’s disclosure that “[p]atients with amenable mutations seemed to demonstrate greater pharmacodynamic response to migalastat HCl compared to patients with non-amenable mutations.”⁴⁸⁰ Dr. Medin is taking this disclosure out of context. Giuliani’s disclosure relates to limited results of nine female Fabry disease patients with eight unique α -Gal A mutations (four responsive and four non-responsive) who were in Phase 2 clinical trials with different dose regimens of migalastat hydrochloride.⁴⁸¹ In my opinion, this limited data cannot be extrapolated to a general statement that all Fabry patients with amenable mutations demonstrate greater pharmacodynamic response to migalastat hydrochloride compared to Fabry patients with non-amenable mutations. Dr. Medin also opines that “Giuliani further discloses categorizing GLA mutations ‘as being amenable or not to migalastat HCl based on an in vitro α -Gal A transfection assay developed in human embryonic kidney (HEK)-293 cells.’”⁴⁸² Giuliani refers to a HEK-293 cell-based assay that was determined to be unreliable at identifying responsive and non-responsive mutations and further, the assay results as to amenability are only disclosed for the eight mutations at issue in the study, and not generally for

⁴⁷⁹ Medin Opening Report, ¶ 244.

⁴⁸⁰ Medin Opening Report, ¶ 246 (quoting Giuliani at Abstract); *see also* Medin Opening Report, ¶ 267 (claim 25), ¶ 278 (claim 26), ¶ 289 (claim 27).

⁴⁸¹ *See* Giuliani at Abstract.

⁴⁸² Medin Opening Report, ¶ 246 (quoting Giuliani at Abstract); *see also* Medin Opening Report, ¶ 267 (claim 25), ¶ 278 (claim 26), ¶ 289 (claim 27).

all amenable mutations. None of the eight mutations in the study appears in Claim 23. In addition, Giugliani refers to the HEK assay that was determined to be unreliable, including because it was used for enrollment in Amicus’s phase 3 clinical studies, which resulted in the 011 study missing its endpoint for the first six months of data. Thus, it is my opinion that Giugliani does not provide any teaching on the α -Gal A mutations from Claim 23.

351. Dr. Medin opines that “Wu also discloses α -galactosidase A mutations that cause Fabry disease.”⁴⁸³ The HEK-293 cell-based assay in Wu was found to be unreliable in identifying responsive and non-responsive mutations. Further, Wu only discloses data for a limited number of specific mutations from in vitro testing and none of those mutations are in Claim 23.

352. Dr. Medin also opines that “Wu discloses the α -galactosidase A HEK 293 assay amenable mutation Q57L.”⁴⁸⁴ Claim 23 does not include the mutation and, therefore, Dr. Medin’s reliance on the disclosures in Wu Table 1 is misplaced. Thus, it is my opinion that Wu does not provide any teaching on the α -Gal A mutations from Claim 23.

353. Dr. Medin also opines that “Germain [2012] also discloses α -galactosidase A mutations that cause Fabry disease.”⁴⁸⁵ This vastly overstates Germain 2012’s disclosures because Germain 2012 merely relates to nine male Fabry disease patients with eight unique α -Gal A mutations, none of which are in Claim 23. As noted above, Germain 2012 refers to the HEK assay that was determined to be unreliable, including because it was used for enrollment in

⁴⁸³ Medin Opening Report, ¶ 247 (citing Wu at 969-70 Table 1).

⁴⁸⁴ Medin Opening Report, ¶ 248 (citing Wu at 969-70 Table 1).

⁴⁸⁵ Medin Opening Report, ¶ 248 (citing Germain 2012 at 3, 5, 9).

Amicus's phase 3 clinical studies, which resulted in the 011 study failing to meet its endpoint for the first six months of data.

354. Dr. Medin next opines that “[i]t was known that mutations in the GLA gene that encode α -galactosidase A (α -Gal A) cause Fabry disease,” and that “[b]y 2011, more than 600 disease-causing mutations in the GLA gene had been identified . . . and by March 2016, more than 800 disease-causing mutations in the GLA gene had been identified”⁴⁸⁶ In my opinion, the high number of unique GLA mutations that had been discovered adds to the complexity of the methods of treatment with migalastat and supports the nonobviousness of Claim 23. In my opinion, it would not have been obvious to try treatment with migalastat for Fabry patients with the specific mutations of Claim 23, especially given the unpredictability of whether or not Fabry patients with a given mutation would respond to treatment with migalastat; further, a person of ordinary skill in the art would not have had a reasonable expectation of success with respect to treating Fabry patients that carry the specific mutations of Claim 23 with migalastat.

355. Dr. Medin opines that “[a]s of the earliest priority date to which the claims of the ’164 patent is entitled, the HEK assay amenable mutations of α -galactosidase A recited in at least Claim 23 would have been obvious to a [person of ordinary skill in the art].”⁴⁸⁷ I disagree. Dr. Medin provides no support for this argument. Further, as of the priority date, there were no Fabry patients discovered to have any of the mutations in Claim 23. Thus, it would not have been obvious to a person of ordinary skill in the art that these yet-to-be discovered mutations were or were not amenable.

⁴⁸⁶ Medin Opening Report, ¶ 249.

⁴⁸⁷ Medin Opening Report, ¶ 249.

356. Dr. Medin opines that “[i]t was well known that migalastat selectively binds and stabilizes α -Gal A, and that a HEK-293 cell-based assay could be used to identify mutant forms of α -Gal A that are responsive to migalastat.”⁴⁸⁸ In my opinion, Dr. Medin has vastly overstated the state of the field at the time the application leading to the ’164 Patent was filed. In fact, the HEK-293 cell-based assay from the ’319 Patent Publication, Wu, Germain 2012, and Giugliani was found to be unable to accurately identify which patients to treat with migalastat. Further, the HEK assay referred to in those references was determined to be unreliable, including because it was used for enrollment in Amicus’s phase 3 clinical studies, which resulted in the 011 study failing to meet its endpoint for the first six months of data. Indeed, pharmacological chaperones were a relatively new avenue of treatment that was being explored. As of the priority date, Galafold® was the one and only FDA approved chaperone for Fabry Disease and it was not until after the invention described in the ’164 Patent that Galafold® was approved to treat Fabry patients with one of the three mutations in Claim 23.⁴⁸⁹

357. Dr. Medin opines that “[t]he prior art further teaches the development of an oral therapy of migalastat HCl for the treatment of Fabry disease . . . and the use of a HEK-293 cell-

⁴⁸⁸ Medin Opening Report, ¶ 249.

⁴⁸⁹ See e.g., Keyzor I., et al., (2023) Therapeutic Role of Pharmacological Chaperones in Lysosomal Storage Disorders: A Review of the Evidence and Informed Approach to Reclassification, *Biomolecules* **13**(8):1227 (“The term “pharmacological chaperone therapy” or “PCT” was first coined in 2000 to describe the category of exogenously administered small molecules that restore folding and trafficking defects of misfolded proteins in LSDs. The EMA approved the first commercially available PCT, migalastat (Galafold®; Amicus Therapeutics Inc., Philadelphia, PA, USA), in 2016, for long-term treatment of adults with Fabry disease who have an amenable mutation (i.e., a mutation that is responsive to treatment).”) (internal citation omitted) (ATGAL_10161626 at -627); May 31, 2016, Amicus Therapeutics Announces European Commission Approval for Galafold™ (Migalastat) in Patients with Fabry Disease in European Union (ATGAL_07336052 at -052); Moran, N., (2018) FDA Approves Galafold, a Triumph for Amicus, *Nat. Biotech.* 36:91 (ATGAL_10161450 at -450).

based assay to identify patients with α -Gal A mutations that are amenable to migalastat treatment.”⁴⁹⁰ For the same reasons explained above, I disagree with this opinion.

358. Dr. Medin opines that “it would have been obvious for a [person of ordinary skill in the art] to simply carry out the steps of a known cell assay to identify the naturally-occurring α -galactosidase A mutations recited in at least Claim 23.”⁴⁹¹ For all of the reasons discussed above, I disagree. Further, Dr. Medin points to no reason why a person of ordinary skill in the art would have found these mutations in particular and been motivated to test these mutations to treat patients with one of those mutations or any reason why a person of ordinary skill in the art would have had a reasonable expectation of success in doing so.

359. Dr. Medin opines that “[a] [person of ordinary skill in the art] would have been motivated with a reasonable expectation of success to combine the teachings of Wu, Germain 2012, Benjamin (2016), and/or Giugliani, at least because each is directed to the use of migalastat in the treatment of Fabry disease and/or the evaluation of mutations in the α -galactosidase A gene in patients with Fabry disease that inform treatment options for Fabry disease, including treatment with migalastat.”⁴⁹² I disagree. In my opinion, a person of ordinary skill in the art would not have combined results or teachings from Benjamin 2016 with those of Wu, Germain 2012, and Giugliani to treat Fabry patients with the specific mutations of Claim 23 because they would have no reason to do it and would not have even been aware of the existence of the mutations in Claim 23. More importantly, even if a person of ordinary skill in the art did combine such references, such person of ordinary skill in the art would not be motivated to reach

⁴⁹⁰ Medin Opening Report, ¶ 250.

⁴⁹¹ Medin Opening Report, ¶ 250.

⁴⁹² Medin Opening Report, ¶ 251, Ex. C at 20-25.

the invention claimed in Claim 23 with any reasonable expectation of success for all of the reasons described above, including, *e.g.*, because none of the mutations at issue in Claim 23 are disclosed in these references as being amenable to migalastat. Dr. Medin also opines that “a [person of ordinary skill in the art] seeking to improve upon existing treatments of Fabry disease would have been motivated with a reasonable expectation of success to combine the disclosures of Wu, and/or Germain 2012 in view of Benjamin (2016) and/or Giugliani, and the knowledge of a [person of ordinary skill in the art].”⁴⁹³ He also opines that “a [person of ordinary skill in the art] would have been motivated to combine the teachings of Wu, Germain 2012, Giugliani, and/or Benjamin (2016) because they all have complementary teachings and show consistent outcomes, therefore, a [person of ordinary skill in the art] would also have an expectation of success in doing so.”⁴⁹⁴ I also disagree with these opinions. Dr. Medin fails to explain exactly which disclosures of Wu, Germain 2012, Benjamin 2016, and Giugliani a person of ordinary skill in the art would combine and why there is a motivation to combine, and why doing so would result in a reasonable expectation of success. Simply saying they have “complementary teachings and show consistent outcomes” does nothing to explain why there would be a reasonable expectation of success. Further, although Dr. Medin mentions knowledge of a person of ordinary skill in the art, he fails to identify what that knowledge is.

⁴⁹³ Medin Opening Report, ¶ 251, Ex. C. 20-25; *see also* Medin Opening Report ¶ 268 (claim 25), ¶ 279 (claim 26), ¶ 290 (claim 27).

⁴⁹⁴ Medin Opening Report, ¶ 252, Ex. C at 19-20; *see also* Medin Opening Report ¶ 268 (claim 25), ¶ 279 (claim 26), ¶ 290 (claim 27).

360. Dr. Medin opines that “Wu discloses the administration of ‘a dose of 150 mg [migalastat hydrochloride] every other day’ as a potential treatment for Fabry disease”⁴⁹⁵

Dr. Medin overstates what Wu discloses. Wu actually discloses that:

The degree of consistency found in the current comparison of HEK-293 cell-based and in vivo mutant α -GAL A responses does not necessarily indicate the degree of consistency that would be seen with any particular dose or regimen of [migalastat hydrochloride]. This is because the in vivo α -GAL A responses analyzed here were obtained following different [migalastat hydrochloride] doses (50, 150, or 250 mg) and with various regimens (every other day, twice per day, or every day), according to the different clinical study protocols.⁴⁹⁶

In my opinion, this is a disclosure of specific doses and dose regimens provided to a limited number of specific Fabry patients with specific mutations. It does not disclose that any such dosages or regimens could be used to treat Fabry patients with other α -Gal A mutations or that a specific dose or regimen is recommended for Fabry patients with the mutations in Claim 23.

361. Dr. Medin opines that Germain 2012 discloses “oral administration of 150 mg migalastat HCl every other day.”⁴⁹⁷ Dr. Medin again overstates this disclosure because like Wu, Germain 2012 relates to treatment of a limited number of specific Fabry patients with specific Fabry mutations at specific doses and dose regimens. It does not disclose that a specific dose or regimen is recommended for Fabry patients with the mutations in Claim 23.

362. Dr. Medin opines that Giuliani discloses “treatment of Fabry Disease patients with 150 or 250 mg migalastat hydrochloride every other day.”⁴⁹⁸ Dr. Medin again overstates this disclosure because like Wu and Germain 2012, Giuliani relates to treatment of a limited number of specific Fabry patients with specific Fabry mutations at specific doses and dose

⁴⁹⁵ Medin Opening Report, ¶ 238 (citing Wu at 974).

⁴⁹⁶ Wu at 975.

⁴⁹⁷ Medin Opening Report, ¶ 238 (citing Germain 2012 at Abstract).

⁴⁹⁸ Medin Opening Report, ¶ 238 (citing Giuliani at Abstract).

regimens. It does not disclose that a specific dose or regimen is recommended for Fabry patients with the mutations in Claim 23.

363. Dr. Medin opines that Benjamin 2016 discloses administration of “150 mg migalastat hydrochloride every other day.”⁴⁹⁹ Dr. Medin’s reliance on Benjamin 2016 is also misplaced because Benjamin 2016 does not disclose treatment of Fabry patients with the mutations in Claim 23 of the ’164 Patent, nor does it disclose use of 150 mg every other day with respect to this mutation. In fact, Benjamin 2016 does not identify any amenable mutation based on the Migalastat Amenability Assay.

364. Dr. Medin opines that “[a]rriving at 123 mg free base equivalent of migalastat or a salt thereof for every other day dosing would be a matter of routine experimentation for a [person of ordinary skill in the art].”⁵⁰⁰ Dr. Medin provides no support for this opinion.

365. Dr. Medin opines that “[a] [person of ordinary skill in the art] would have been motivated to combine the teachings of Wu, Germain 2012, Giugliani, and/or Benjamin (2016) to arrive at 123 mg free base equivalent every other day dosing because they all have complementary teachings and show consistent outcomes, therefore, a [person of ordinary skill in the art] would also have an expectation of success given these complementary teachings and using routin[e] experimentation.”⁵⁰¹ I disagree. Dr. Medin fails to explain exactly which disclosures of Wu, Germain 2012, Benjamin 2016, and Giugliani a person of ordinary skill in the art would combine and why there is a motivation to combine, and why doing so would result in a reasonable expectation of success. Simply saying they have “complementary teachings and

⁴⁹⁹ Medin Opening Report, ¶ 238 (citing Benjamin at 4).

⁵⁰⁰ Medin Opening Report, ¶ 238.

⁵⁰¹ Medin Opening Report, ¶ 239; *see also* Medin Opening Report ¶ 269 (claim 25), ¶ 280 (claim 26), ¶ 291 (claim 27).

show consistent outcomes” does nothing to explain why there would be a reasonable expectation of success. Further, although Dr. Medin mentions knowledge of a person of ordinary skill in the art, he fails to identify what that knowledge is.

366. It is unclear what combination(s) Dr. Medin is even relying upon for his analysis of Claim 23. Because Dr. Medin’s obviousness combinations are unclear, I reserve the right to supplement my opinions based on any additional and/or clarifying opinions that Dr. Medin renders with respect to Claim 23. Further, Dr. Medin fails to identify what he is using as his base reference, how he is modifying it and what reference he is modifying it with, and why a person of ordinary skill in the art would be motivated to modify the reference or have had a reasonable expectation of success in such a combination. Dr. Medin more generally fails to explain how he is combining the prior art references and how and why, in his opinion, such references would cause a person of ordinary skill in the art to reach the claimed invention. In addition, he generally fails to acknowledge the fact that the prior art references he relies on do not disclose treating Fabry patients with the specific mutations in Claim 23 and he fails to explain how a person of ordinary skill in the art would reach such a method of treatment for those specific mutations based on the references he relies upon.

367. Dr. Medin generally fails to acknowledge the fact that the prior art references he relies on do not disclose treating Fabry patients with the specific mutations in Claim 23 and he fails to explain how a person of ordinary skill in the art would reach such a method of treatment for those specific mutations based on the references he relies upon, why a person of ordinary skill in the art would combine them, and why such a person of ordinary skill in the art would have a reasonable expectation of success in doing so.

2. Claim 24

368. Claim 24 of the '164 Patent (bolded below) depends from Claim 23. The claim language is:

23. A method for treatment of Fabry disease in a human patient in need thereof, the method comprising orally administering to the patient about 123 mg free base equivalent of migalastat or a salt thereof every other day, wherein the patient has an α -galactosidase A mutation selected from the group consisting of: Y184S, N228H, or T412I.

24. The method of claim 23, wherein the patient is administered about 150 mg of migalastat hydrochloride every other day.

369. Based on my review of Dr. Medin's report, it is unclear what combinations Dr. Medin asserts for Claim 24. Dr. Medin lists only the following combinations in the summary of his opinions:

- 1) The '319 patent publication in view of Lockhart '093 and the knowledge of a person of ordinary skill in the art;
- 2) Wu, Germain [2012], Benjamin 2016, and/or Giugliani and the knowledge of a person of ordinary skill in the art;
- 3) Wu and/or Germain [2012] in view of Benjamin 2016 and/or Giugliani and the knowledge of a person of ordinary skill in the art.⁵⁰²

370. Regarding the first combination—Dr. Medin did not identify what knowledge a person of ordinary skill in the art would have had that is relevant to this combination or why a person of ordinary skill in the art would have been motivated to use that knowledge to modify what is disclosed in the '319 Patent Publication.

371. Regarding the second combination—Wu, Germain 2012, Benjamin, and/or Giugliani, and the knowledge of a person of ordinary skill in the art—it is unclear exactly which of those references he is combining and how those references are being combined. Dr. Medin

⁵⁰² Medin Opening Report, ¶ 13.

discusses each of the four references individually before alleging in a conclusory fashion that they could be combined with no explanation of how they would be combined.⁵⁰³ Dr. Medin again failed to identify what knowledge a person of ordinary skill in the art would have had that is relevant to this combination or why a person of ordinary skill in the art would have been motivated to use that knowledge to modify what is disclosed in the references cited by Dr. Medin.

372. Regarding the third combination—Wu and/or Germain 2012 in view of Benjamin 2016 and/or Giugliani and the knowledge of a person of ordinary skill in the art—it is unclear exactly which of those references he is combining and how those references are being combined. Like with the second combination, Dr. Medin discusses each of the four references individually before alleging in a conclusory fashion that they would be combined, with no explanation of how they would be combined or why a person of ordinary skill in the art would combine them. Again, Dr. Medin failed to identify what knowledge a person of ordinary skill in the art would have had that is relevant to this combination or why a person of ordinary skill in the art would have been motivated to use that knowledge to modify what is disclosed in the references cited by Dr. Medin.

373. In my opinion, as discussed further below, Dr. Medin’s combinations do not disclose the limitations of Claim 24 and do not render Claim 24 obvious.

⁵⁰³ See Medin Opening Report, ¶ 258 (“A POSA [person of ordinary skill in the art] would have been motivated to combine the teachings of Wu, Germain [2012], Giugliani and/or Benjamin (2016) for this dosing because they all have complementary teachings and show consistent outcomes, therefore, a POSA [person of ordinary skill in the art] would also have an expectation of success in doing so.”); *see also* Medin Opening Report ¶ 269 (claim 25), ¶ 280 (claim 26), ¶ 291 (claim 27).

374. I incorporate by reference my analysis of Claim 23 set forth above. I address the remaining limitations of Claim 24 below.

375. In my opinion, Claim 24 would not have been obvious over Dr. Medin's asserted prior art combinations for the same reasons that I discuss with respect to these references in Claim 23.

a) Asserted Combination 1: the '319 Patent Publication in view of Lockhart '093 and the Knowledge of a Person of Ordinary Skill in the Art

376. For the additional limitations of Claim 24, Dr. Medin opines that "Lockhart '093 discloses administering the hydrochloride salt of DGJ (i.e., migalastat) to participants at a specified dose level of 150 mg every other day."⁵⁰⁴ In my opinion, Dr. Medin overstates the disclosures in Lockhart '093. Lockhart '093 does not disclose that a dose of 150 mg every other day will work for all α -Gal A mutations or even for all amenable mutations. Further, Lockhart '093 does not disclose that 150 mg every other day is an effective dose for Fabry patients with any of the mutations in Claim 24. Dr. Medin relies upon Lockhart '093's discussion of modeling of doses related to IFG and the disclosure that such model could be applicable to DGJ.⁵⁰⁵ This theoretical model does not provide a motivation to treat a Fabry patient with a specific dosage, especially in light of the many other dose regimens discussed in Lockhart '093, including in the Examples 4-6 that Dr. Medin cites.⁵⁰⁶

377. Dr. Medin opines that "[a] [person of ordinary skill in the art] would have been aware of the 150 mg every other day dosing of migalastat to treat Fabry Disease and its

⁵⁰⁴ Medin Opening Report, ¶ 254 (citing Lockhart '093, ¶ 0151, Exs. 4-6), Ex. C at 21.

⁵⁰⁵ Lockhart '093, ¶¶ 0142, 0151.

⁵⁰⁶ Lockhart '093, ¶¶ 0142, 0151; *see also supra* § VIII.A.5.

effectiveness from at least Lockhart '093, and therefore would have been motivated to rely on this teaching to arrive at the 150 mg every other day dosing.”⁵⁰⁷ Dr. Medin also opines that “[a] [person of ordinary skill in the art] would further have had an expectation of success with this dosing given the teachings of Lockhart '093.”⁵⁰⁸ I disagree with these opinions. Lockhart '093 does not disclose that 150 mg every other day is an effective dose for all Fabry patients or for all Fabry patients with an amenable mutation. Nor does Lockhart '093 even suggest that 150 mg every other day is the preferred dose and dose regimen of migalastat hydrochloride for any Fabry patient. Lockhart '093 relies on theoretical dosing models and preliminary data for enrollment of phase 2 studies related to migalastat hydrochloride where a number of different doses and dose regimens were used.⁵⁰⁹ A person of ordinary skill in the art would have understood Lockhart '093 to be a preliminary investigation into dosing of pharmacological chaperones like migalastat hydrochloride and not some definitive reference of the proper dose of migalastat hydrochloride for all Fabry patients, as Dr. Medin suggests.

378. Dr. Medin then opines that “claims 24 would have been obvious over the '319 patent publication in view of Lockhart and the knowledge of a [person of ordinary skill in the art].”⁵¹⁰ In my opinion, Dr. Medin has failed to show Claim 24 of the '164 Patent is obvious over the '319 Patent Publication in view of Lockhart '093 and the knowledge of a person of ordinary skill in the art. For all the reasons discussed herein, in my opinion, Dr. Medin has failed to prove that Claim 24 is obvious. Based on my review of the prior art references and the disclosures cited, in my opinion, Claim 24 is not obvious and there is no motivation to combine

⁵⁰⁷ Medin Opening Report, ¶ 255, Ex. C at 21.

⁵⁰⁸ Medin Opening Report, ¶ 255.

⁵⁰⁹ See Lockhart '093, Exs. 4-6.

⁵¹⁰ Medin Opening Report, ¶ 256.

the references with any reasonable expectation of success in reaching the invention of Claim 24. Dr. Medin generally fails to acknowledge the fact that the prior art references he relies on do not disclose treating Fabry patients with the specific mutations in Claim 24 and he fails to explain how a person of ordinary skill in the art would reach such a method of treatment for those specific mutations based on the references he relies upon, why a person of ordinary skill in the art would combine them, and why such a person would have a reasonable expectation of success in doing so.

b) Asserted Combination 2: Undisclosed Combination of Wu, Germain 2012, Giugliani, and/or Benjamin 2016 and the Knowledge of a Person of Ordinary Skill in the Art;

and

Asserted Combination 3: Wu and/or Germain 2012 in View of Benjamin 2016 and/or Giugliani and the Knowledge of a Person of Ordinary Skill in the Art

379. For the additional limitations of Claim 24, Dr. Medin opines that “Wu discloses the administration of ‘a dose of 150 mg [migalastat hydrochloride] every other day’ as a potential treatment for Fabry disease.”⁵¹¹ Dr. Medin overstates what Wu discloses. Wu actually discloses that:

The degree of consistency found in the current comparison of HEK-293 cell-based and in vivo mutant α -GAL A responses does not necessarily indicate the degree of consistency that would be seen with any particular dose or regimen of [migalastat hydrochloride]. This is because the in vivo α -GAL A responses analyzed here were obtained following different [migalastat hydrochloride] doses (50, 150, or 250 mg) and with various regimens (every other day, twice per day, or every day), according to the different clinical study protocols.⁵¹²

⁵¹¹ Medin Opening Report, ¶ 257 (citing Wu at 974), Ex. C at 21.

⁵¹² Wu at 975.

In my opinion, this is a disclosure of specific doses and dose regimens provided to a limited number of specific Fabry patients with specific mutations. It does not disclose that any such dosages or regimens could be used to treat Fabry patients with other α -Gal A mutations or that a specific dose or regimen is recommended for Fabry patients with the mutations in Claim 24.

380. Dr. Medin opines that Germain 2012 discloses “oral administration of 150 mg migalastat HCl every other day.”⁵¹³ Dr. Medin again overstates this disclosure because like Wu, Germain 2012 relates to treatment of a limited number of specific Fabry patients with specific Fabry mutations at specific doses and dose regimens. It does not disclose that a specific dose or regimen is recommended for Fabry patients with the mutations in Claim 24.

381. Dr. Medin opines that Benjamin 2016 discloses “administration of 150 mg migalastat HCl.”⁵¹⁴ Dr. Medin’s reliance on Benjamin 2016 is also misplaced because Benjamin 2016 does not disclose treatment of Fabry patients with the mutations in Claim 24 of the ’164 Patent, nor does it disclose use of 150 mg every other day with respect to this mutation. In fact, Benjamin 2016 does not identify any amenable mutation based on the Migalastat Amenability Assay.

382. Dr. Medin opines that “[a] [person of ordinary skill in the art] would have been motivated to combine the teachings of Wu, Germain 2012, Giugliani, and/or Benjamin (2016) for this dosing because they all have complementary teachings and show consistent outcomes, therefore, a [person of ordinary skill in the art] would also have an expectation of success in doing so.”⁵¹⁵ I disagree. Dr. Medin fails to explain exactly which disclosures of Wu, Germain

⁵¹³ Medin Opening Report, ¶ 257 (citing Germain 2012 at Abstract), Ex. C at 21.

⁵¹⁴ Medin Opening Report, ¶ 257 (citing Benjamin at 4), Ex. C at 21.

⁵¹⁵ Medin Opening Report, ¶ 258, Ex. C at 21-22.

2012, Benjamin 2016, and Giugliani a person of ordinary skill in the art would combine and why there is a motivation to combine, and why doing so would result in a reasonable expectation of success. Simply saying they have “complementary teachings and show consistent outcomes” does nothing to explain why there would be a reasonable expectation of success. Further, although Dr. Medin mentions knowledge of a person of ordinary skill in the art, he fails to identify what that knowledge is.

383. It is unclear what combination(s) Dr. Medin is even relying upon for his analysis of Claim 24. Because Dr. Medin’s obviousness combinations are unclear, I reserve the right to supplement my opinions based on any additional and/or clarifying opinions that Dr. Medin renders with respect to Claim 24. Further, Dr. Medin fails to identify what he is using as his base reference, how he is modifying it and what reference he is modifying it with, and why a person of ordinary skill in the art would be motivated to modify the reference or have had a reasonable expectation of success in such a combination. Dr. Medin more generally fails to explain how he is combining the prior art references and how and why, in his opinion, such references would cause a person of ordinary skill in the art to reach the claimed invention. In addition, he generally fails to acknowledge the fact that the prior art references he relies on do not disclose treating Fabry patients with the specific mutations in Claim 24 and he fails to explain how a person of ordinary skill in the art would reach such a method of treatment for those specific mutations based on the references he relies upon.

384. Dr. Medin opines that “claim 24 would have been obvious to a [person of ordinary skill in the art] over Wu and/or Germain 2012 in view of Benjamin (2016), and/or Giugliani, and the knowledge of a [person of ordinary skill in the art].”⁵¹⁶ In my opinion, Dr.

⁵¹⁶ Medin Opening Report, ¶ 259.

Medin has failed to prove that Claim 24 is obvious. Based on my review of the prior art references and the disclosures cited, in my opinion, Claim 24 is not obvious and there is no motivation to combine the references with any reasonable expectation of success in reaching the invention of Claim 24. Dr. Medin generally fails to acknowledge the fact that the prior art references he relies on do not disclose treating Fabry patients with the specific mutations in Claim 24 and he fails to explain how a person of ordinary skill in the art would reach such a method of treatment for those specific mutations based on the references he relies upon, why a person of ordinary skill in the art would combine them, and why such a person would have a reasonable expectation of success in doing so.

3. Claim 25

385. Claim 25 of the '164 Patent (bolded below) depends from Claim 23. The claim language is:

23. A method for treatment of Fabry disease in a human patient in need thereof, the method comprising orally administering to the patient about 123 mg free base equivalent of migalastat or a salt thereof every other day, wherein the patient has an α -galactosidase A mutation selected from the group consisting of: Y184S, N228H, or T412I.

25. The method of claim 23, wherein the patient has the mutation Y184S.

386. I incorporate by reference my analysis with respect to Claim 23, which also applies to the opinions that Dr. Medin renders for Claim 25.

387. Claim 25 narrows the list of mutations from three (Y184S, N228H, or T412I) to one (Y184S). For the same reasons that Claim 23 is not obvious over Dr. Medin's asserted prior art references, Claim 25 is also not obvious.

388. My opinions with respect to Dr. Medin's opinions for Claim 23 also demonstrate why Claim 25 is not obvious over Dr. Medin's asserted combinations.

4. Claim 26

389. Claim 26 of the '164 Patent (bolded below) depends from Claim 23. The claim language is:

23. A method for treatment of Fabry disease in a human patient in need thereof, the method comprising orally administering to the patient about 123 mg free base equivalent of migalastat or a salt thereof every other day, wherein the patient has an α -galactosidase A mutation selected from the group consisting of: Y184S, N228H, or T412I.

26. The method of claim 23, wherein the patient has the mutation N228H.

390. I incorporate by reference my analysis with respect to Claim 23, which also applies to the opinions that Dr. Medin renders for Claim 26.

391. Claim 26 narrows the list of mutations from three (Y184S, N228H, or T412I) to one (N228H). For the same reasons that Claim 23 is not obvious over Dr. Medin's asserted prior art references, Claim 26 is also not obvious.

392. My opinions with respect to Dr. Medin's opinions for Claim 23 also demonstrate why Claim 26 is not obvious over Dr. Medin's asserted combinations.

5. Claim 27

393. Claim 27 of the '164 Patent (bolded below) depends from Claim 23. The claim language is:

23. A method for treatment of Fabry disease in a human patient in need thereof, the method comprising orally administering to the patient about 123 mg free base equivalent of migalastat or a salt thereof every other day, wherein the patient has an α -galactosidase A mutation selected from the group consisting of: Y184S, N228H, or T412I.

27. The method of claim 23, wherein the patient has the mutation T412I.

394. I incorporate by reference my analysis with respect to Claim 27, which also applies to the opinions that Dr. Medin renders for Claim 27.

395. Claim 27 narrows the list of mutations from three (Y184S, N228H, or T412I) to one (T412I). For the same reasons that Claim 23 is not obvious over Dr. Medin's asserted prior art references, Claim 27 is also not obvious.

396. My opinions with respect to Dr. Medin's opinions for Claim 23 also demonstrate why Claim 27 is not obvious over Dr. Medin's asserted combinations.

G. Objective Indicia of Nonobviousness

397. I understand that consideration of any objective indicia of nonobviousness is a required part of the obviousness analysis. Dr. Medin states that he is "not aware of the existence of any such considerations."⁵¹⁷ I understand that Amicus has provided evidence related to such objective indicia of nonobvious, but that Dr. Medin has failed to consider such evidence in his report. For this reason alone, I understand that Dr. Medin's obviousness analysis fails. To the extent Dr. Medin later renders an opinion as to objective indicia of nonobviousness, I reserve the right to respond to such opinion.

398. In addition, I have reviewed the opening expert report of Dr. John Jefferies, which relates to this topic. I agree with the opinions in Dr. Jefferies' opening report.

IX. THE ASSERTED CLAIMS INVOLVE MORE THAN THE PERFORMANCE OF WELL-UNDERSTOOD, ROUTINE, AND CONVENTIONAL ACTIVITIES PREVIOUSLY KNOWN TO THE INDUSTRY

399. I have been asked to opine as to whether methods of treating certain Fabry patients with migalastat claimed in the Asserted Claims were well-understood, routine, and conventional as of the priority dates of each Asserted Claim.

⁵¹⁷ Medin Opening Report, ¶ 294.

A. Reassessment Patents

400. At the time of their priority date (which I have been informed in May 30, 2017), the Reassessment Patent Claims provided a novel method of treating Fabry disease patients having mutations identified in the Reassessment Patent Claims.

401. As of May 30, 2017, there was only one FDA-approved treatment for Fabry disease, which was enzyme replacement therapy (“ERT”), i.e. agalsidase beta (FABRZYME), which was approved by the FDA in April 2003.⁵¹⁸

402. Prior to the approval of GALAFOLD (migalastat), using Fabrazyme to treat all Fabry patients was the only approved treatment available in the United States.

403. It was not well-understood, routine, or conventional to use migalastat to treat Fabry disease patients who have a mutation of the Reassessment Patent Claims by May 30, 2017, the priority date of those patents.

404. The FDA did not approve GALAFOLD (migalastat) for the treatment of Fabry disease for adults until August 10, 2018.⁵¹⁹

405. Even though a person of ordinary skill in the art may have known that migalastat was undergoing clinical trials and being studied as a potential treatment, migalastat would not have been a standard treatment for Fabry disease in a patient, as no physicians would have been prescribing it yet. The only way Fabry disease patients would have been treated using migalastat, to my knowledge, was in the clinical trials, and a person of ordinary skill in the art

⁵¹⁸ See, e.g., May 2010 FABRAZYME Prescribing Information (ATGAL_09687616 at -616); see also ’388 Patent at 2:5-13 (“Two *a*-Gal A products are currently available for the treatment of Fabry disease: agalsidase alfa (Replagal®, Shire Human Genetic Therapies) and agalsidase beta (Fabrazyme®; Sanofi Genzyme Corporation).”).

⁵¹⁹ Aug. 10, 2018 FDA News Release, FDA Approves New Treatment for a Rare Genetic Disorder, Fabry Disease (ATGAL_09880475 at -475).

would not have considered such clinical trial treatments to be well-understood, routine, and conventional.

406. It is also my opinion that it was not well-understood, routine, or conventional to be able to accurately identify which Fabry patients would be treatable with migalastat by the priority date of the Reassessment Patents.

407. More specifically, a person of ordinary skill in the art would not have found it well-understood, routine, and conventional to treat Fabry disease in a patient by administering migalastat to a patient having an α -GALA protein with one of the following mutations:

- for the '388 Patent Claim 8, A13P, A20D, Q57L, G80D, P146S, D175E, K213M, I242F, M267T, A309V, V316I, V316G, P323R, A352G, R356P, T385A, V390M, and G395A
- for the '388 Patent Claim 36, G80D, P146S, M267T, and R356P
- for the '489 Patent Claim 17, A13T, N34T, M42K, L54F, P60T, E87D, L89F, Y123C, H125L, I133M, K140T, F145S, P146R, Y152H, D165G, p.M187_S188dup, V199G, M208R, I219L, N224T, Q250R, G261C, G271D, M284V, I303F, D322N, G325R, K326N, G334E, E358Q, E358D, G361E, G375E, T412N and M421V
- for the '489 Patent Claim 23, L54F, L89F, K140T and G334E
- for the '490 Patent Claim 9, I242F, G334E, N34D and p.V254del.

408. Prior to the GLP-HEK assay and the work of Amicus, the only available methods of identifying Fabry disease mutations that could be responsive to migalastat were not reliable.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] 520

409. It is my opinion that as of May 30, 2017, prior to the disclosure of the Reassessment Patents, a person of ordinary skill in the art would not have been able to use the GLP-HEK assay to identify the specific mutations that were amenable to treatment with migalastat. This is because nothing in the prior art, including but not limited to Benjamin 2016, contained enough detail for a person of ordinary skill in the art to use the GLP-HEK assay to identify Fabry patients that can be treated with migalastat. For example, Benjamin 2016 discloses that the GLP-HEK assay is bioanalytically validated, but does not disclose what particular steps a person of skill would need to take in order to validate the assay.

410. It is also my opinion that a person of ordinary skill in the art would have been unable to identify which mutations are amenable to migalastat treatment based on Benjamin 2016 because Benjamin 2016 did not include a list of amenable mutations. Instead, Benjamin 2016 discloses that “600 FD mutations have been tested; 268 have met the amenable mutation criteria.”⁵²¹ Therefore, it would not have been well-understood, routine, or conventional for a person of ordinary skill in the art to use migalastat to treat Fabry patients with the specific mutations of the Reassessment Patents, in part because a person of ordinary skill in the art would not have been able to identify the claimed mutations as being treatable by migalastat as of the priority date of the Reassessment Patents.

520 [REDACTED]

⁵²¹ Benjamin 2016 at 3-4.

B. Engineered Mutations Patent

411. It is my opinion that it was not well-understood, routine, or conventional to use migalastat to treat Fabry disease patients that have the α -Gal A protein with the Y184S, N228H, or T412I mutations, by August 7, 2019, which I understand is the priority date of the Engineered Mutations Patent.

412. As of the August 7, 2019 priority date of the Engineered Mutations Patent, the FDA had approved GALAFOLD (migalastat) for less than one year. GALAFOLD was approved on August 10, 2018.⁵²² Despite GALAFOLD being FDA approved, enzyme replacement therapy was still widely used for the treatment of Fabry patients.

413. Even though there were some Fabry disease patients being treated by migalastat as of the priority date of the Engineered Mutations Patent, a person of ordinary skill would know that treatment with migalastat is only appropriate for patients with an amenable mutation, and not all Fabry patients. For a physician to consider using migalastat as a method of treatment, the physician would have to first identify the patient's mutation and then confirm its amenability to migalastat treatment.

414. It is my opinion that a person of ordinary skill in the art would not have considered migalastat to be a well-understood, routine, or conventional treatment of Fabry disease for the Y184S, N228H, or T412I mutations, as of the priority date of the Engineered Mutations Patent. This is because, until Amicus's work in the Engineered Mutations Patent, (1) Y148S, N228H, and T412I α -Gal A mutations were not previously associated with Fabry disease; and (2) a person of ordinary skill in the art would not have known that these mutations

⁵²² Aug. 10, 2018 FDA News Release, FDA Approves New Treatment for a Rare Genetic Disorder, Fabry Disease (ATGAL_09880475 at -475).

were treatable by migalastat. As the specification states, the inventors of the Engineered Mutations Patent “unexpectedly discovered that the low α -Gal A activity resulting from the missense mutations in α -Gal A shown in Table 2 [including Y148S, N228H, and T412I] can be increased when exposed to pharmacological chaperones, even though no patients have previously been identified with these particular mutations,” and thus, patients with Y148S, N228H, and T412I mutations were “expected to be responsive to treatment with pharmacological chaperones.”⁵²³ The invention of the asserted claims of the Engineered Mutations Patent prevented delay in treatment of Fabry, “as further testing of the PC amenability of the patient’s α -Gal A is no longer necessary.”⁵²⁴ “Instead, after determining the patient’s particular mutation, the clinician can consult a list of α -Gal A mutations (e.g. including one or more mutations listed in Table 2 [including Y148S, N228H, and T412I]) and, if the patient’s mutation is in the list, can begin treatment immediately.”⁵²⁵ Amicus’s work also allowed for the determination of “whether a subject, including an embryo or a neonatal infant, is at risk of developing Fabry disease before the appearance of symptoms.”⁵²⁶

X. CONCLUSION

415. For all the reasons outlined and explained in this report, each of the Asserted Claims of the ’388, ’489, ’490, and ’164 Patents are not obvious over the prior art combinations that Dr. Medin presents in his opening report.

⁵²³ ’164 patent 19:62–20:3.

⁵²⁴ ’164 patent 20:5–10.

⁵²⁵ ’164 patent 20:5–10.

⁵²⁶ ’164 patent 20:11–14.

416. Moreover, the method of each of the asserted claims of the '388, '489, '490, and '164 Patents contain elements that were not well-understood, routine, and conventional as of the priority dates of the Asserted Patents.

XI. SUPPLEMENTATION

417. I reserve the right to amend or supplement the opinions expressed in this report in light of additional materials or information that may come to my attention, including any critique of my report or my opinions advanced by or on behalf of Aurobindo.

418. In addition, I may rely on visual aids and/or demonstrative exhibits to demonstrate the bases of my opinions. Examples of these visual aids and demonstrative exhibits may include, for example, claim charts, patent drawings, excerpts from patent specifications, file histories, deposition testimony, and deposition exhibits, as well as physical exhibits, test data, charts, photographs, diagrams, videos, and animated or computer-generated graphics.

I declare under penalty of perjury that the foregoing is true and correct.

Dated: May 2, 2025.



ROBERT HOPKIN, M.D.

EXHIBIT 1

HOPKIN, ROBERT J

Curriculum Vitae

1. **Name and personal data :**

Robert J. Hopkin, M.D.
3333 Burnet Avenue, ML 4006
Cincinnati, OH 45229-3039

Work phone: (513) 636-4760
Email: rob.hopkin@cchmc.org

Fax: (513) 636-7297

2. **Education:**

<u>Institution and location</u>	<u>Degree</u>	<u>Year</u>	<u>Field of Study</u>
Brigham Young University Provo, UT	B.S.	1986	Zoology
University of Nevada School of Medicine Reno, NV	M.D.	1990	Medicine
Phoenix Children's Hospital Maricopa Medical Center Pediatric Residency Program, Phoenix, Arizona		1990-1993	Pediatric Residency
Phoenix Children's Hospital Maricopa Medical Center Pediatric Residency Program, Phoenix, Arizona,		1993-1994	Chief Residency
Children's Hospital Medical Center Cincinnati, OH		1994-1997	Fellowship in Human Genetics

3. **Academic appointments:**

Instructor of Clinical Pediatrics, Division of Human Genetics
Children's Hospital Medical Center
Cincinnati, Ohio, 1997-2000

Instructor of Clinical Pediatrics, Division of Human Genetics
University of Cincinnati College of Medicine Department of Pediatrics
Cincinnati Ohio, July 1997-June 2000

Assistant Professor of Clinical Pediatrics, Division of Human Genetics
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio, 2000-2008

HOPKIN, ROBERT J

Assistant Professor of Clinical Pediatrics, Division of Human Genetics
University of Cincinnati College of Medicine Department of Pediatrics
Cincinnati Ohio, July 2000-June 2008

Assistant Professor, clinical, Department of Analytical & Diagnostic Sciences, College of
Allied Health Sciences, University of Cincinnati, Cincinnati, Ohio 2002-2008

Associate Professor of Clinical Pediatrics, Division of Human Genetics
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio, 2008-October 2022

Associate Professor of Clinical Pediatrics, Division of Human Genetics
University of Cincinnati College of Medicine Department of Pediatrics
Cincinnati Ohio, July 2008-October 2022

Associate Professor, clinical, Department of Analytical & Diagnostic Sciences, College of
Allied Health Sciences, University of Cincinnati, Cincinnati Ohio 2008-2011

Professor of Clinical Pediatrics, Division of Human Genetics Cincinnati Children's Hospital
Medical Center, Cincinnati Ohio, 25 October 2022-present

Professor of Clinical Pediatrics, University of Cincinnati College of Medicine Department of
Pediatrics Division of Human Genetics Cincinnati Ohio, 25 October 2022-present
Cincinnati Ohio

4. Licensing and Certification

Ohio medical license 35.066579 1994-present
NPI 1447281878 expiration 10/01/2026

Clinical Genetics:

American Board of Medical Genetics, September 27, 1996 # 96077

Recertified 2006;

MOC recertification Dec 31, 2019 Current for the 2024 cycle Expiration dates no longer
provided

Pediatrics:

American Board of Pediatrics October 13, 1993 # 51159

Recertified in 2000

Recertified October 2007

Recertified 2014 MOC;

Recertified Dec 31, 2017

MOC Recertification Dec. 31, 2019 expires 2029

Citi: Initial certification 7/7/2009 Last updated 12/21/2024

HOPKIN, ROBERT J

5. Awards and honors:

1. Outstanding Medical Research While in Pediatric Residency Training, 1994
2. Teacher of the year, Cincinnati Children's Hospital Medical Center, 2001
3. Fabry Physician Award 2016 from the Fabry Support and Information Group
4. RARE Champion of Hope Nominee, Medical Care & Treatment 2017
5. National Fabry Disease Foundation award of appreciation 2018
6. Cincinnati Top Docs Genetics 2014, 2015, 2016, 2018, 2019, 2020, 2021
7. CCHMC Hidden Gems Award 2021
8. CCHMC Outstanding Research Team award as a member of the NF Team 2021

6. Clinical service

Clinical Expertise and activities

I am broadly interested in Genetic disease. Key factors in provision of excellent genetic services includes the ability to use state of the art as well as older established diagnostic tools appropriately (chromosome analysis through whole Genome sequence and beyond). However, in my mind establishing the diagnosis is only an initial step. Long term follow up is needed to make interventions and set or update therapeutic goals. I am involved in a variety of focused clinics as well as general genetics clinics:

DSD Center I was part of the founding of this clinic and am geneticist who sees the vast majority of the patients in the clinic. I am also involved with genetics in the DSD TRN which is a national DSD organization. Patients come for evaluation from Ohio, Kentucky, Indiana, West Virginia and occasionally from other states.

22q11.2 Center I was part of founding this multidisciplinary clinic over 10 years ago. I am one of 2 geneticist who see the 200 patients with 22q11.3 deletion followed in this center. We see patients from throughout Ohio, Indiana, Kentucky and West Virginia. The Center has been coordinated through the Division of Human Genetics but includes cardiology, immunology, ENT, Endocrinology, plastic surgery, and other specialties need for care of this population. I have several publications on 22q11.2 deletion in the past and have been one of the local leaders in the Center since it was started over 15 years ago.

Lysosomal Disease Center: Fabry, Gaucher, Pompe, MPS I, MPS II, Other MPS, NPC, etc. We see patients from a larger region for this clinic and see many adult as well as pediatric patients. We are also a nationally recognized center that is often consulted for complex issues involving management of lysosomal disease especially Fabry disease. I am the physician provider for Fabry disease, Gaucher disease, and see smaller numbers of patients with the other conditions. We are involved in clinical research, clinical trials.

NF1, NF2, and Schwannomatosis clinic Cincinnati Children's Hospital has been one of the major centers care and management of Neurofibromatosis types 1 and 2 and schwannomatosis for 30 years. I have been a part of the development since 1994. I am one

HOPKIN, ROBERT J

of 2 clinical geneticists currently involved in the clinic. We are currently looking for a new clinical director. We have provided care for thousands of patients with neurofibromatosis and have been involved in developing standards of care for bone disease, plexiform neurofibromas, brain tumors, developmental disability and other manifestations of this important group of diseases. This is also a multidisciplinary effort with Hematology Oncology, Orthopedics, Neurology, Neurosurgery, Endocrinology, and some basic scientists also participating. We are a nationally recognized center of excellence for NF1.

Craniofacial (mostly infant and toddler) clinic, this is a long term interest of mine and a strength of CCHMC. Our center is a leader on a national basis. I have been a member of the team but have not taken key leadership roles. I am currently seeing patients only when needed and not participating regularly in the formal multidisciplinary clinics. I have been an investigator on multiple publications for craniofacial disorders from relatively common (cleft lip and cleft palate) to newly discovered entities like Acrofacial Dysostosis, Cincinnati Type.

CHARGE syndrome Center I was one of the founding members of this clinic and am still involved although Brittany Simpson is now the leading Geneticist in this Center. I have been one of her mentors and still see multiple patients with CHARGE syndrome each year. This is a unique resource at CCHMC since there have been no other active centers with a focus on CHARGE syndrome. We are currently helping several other centers develop services using a similar approach. This is the leading center in the USA for care of CHARGE syndrome.

Fetal Care Center I was one of the founding members of the Fetal Care center and have continued to see patients mainly for genetic diagnostics and prognosis. I am also frequently involved in postnatal follow up for the children after delivery. My time commitment to this service has decreased in the past few years because of the demands from the Lysosomal disease clinic where I have a more central leadership role.

BWS This is not a formal center but is an area of interest. I have published several papers on BWS and see many local and regional patients for BWS. I have been involved in research and development of clinical guidelines on a national basis as well.

1p36 deletion in addition to seeing many of the local patients with 1p36 deletion I am a medical advisor for the national support group for this condition and have done several small clinical research projects to help better delineate the natural history and care needs for the affected patients. This is not a formally organized clinic, but it is an area of interest and expertise.

Psychiatry/Genetics in-patient/out-patient services at College Hill. I was the genetic faculty mentor for Amelle Shillington, DO who started this service in collaboration with psychiatry. I am no longer directly involved with this as Amelle Shillington is now a faculty member and taking the lead. I was directly involved for the development of the service as the primary mentor for Dr. Shillington who was a resident at that time.

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General genetics especially very rare diseases: I have also had a long standing interest in general genetics and very rare conditions. Until recently we have not had any formal program with that focus. I have nevertheless tried to recognize unique or new presentations and to do detailed evaluation. As a result I have been an author in the earliest descriptions of a number of conditions. For some of these I had a leading role for others I was one of many contributors. The key in my mind is to recognize and define the conditions well enough to be useful to the families and hopefully to contribute to the scientific understanding of human biology.

The following are 20 conditions in which I participated in one of the early publications with the year of the publications: LAPPS 1998, disorganization phenotype 2001, diaphragmatic eventration and micro-ophthalmia 2002, Proximal 11q duplication 2007, Ermine phenotype 2009, 17p deletion of YWHAE and CRK 2011, Tetrasomy 5q35.2-q35.3 2011, Autosomal dominant COL11A1 severe skeletal dysplasia 2014, Acrofacial Dysostosis, Cincinnati Type (POLR1A) 2015, mandibulofacial dysostosis with alopecia 2015, PACS1 related syndrome 2016, FGFR1 causing Hartsfield syndrome 2016, Mosaic SMO loss of function causing Curry-Jones syndrome 2016, MPDZ related hydrocephalus 2017, MED13 related neurodevelopmental disorder 2018, UPD 16 related imprinting disorder 2019, NMNAT2 related disorder 2019, BMPR1A related disorder 2019, SMPD4 developmental disorder with arthrogryposis 2019, CSDE1 related disorder 2019, CDH2 related syndrome 2019, ACOX1 gain of function 2020.

I have also contributed to expansions of phenotypes, and revisions in understanding of a number of very rare conditions (not listed).

I have been involved as an advisor for several national support groups including:
Fabry Support and Information group
National Fabry Disease Foundation (currently the Chair of the Medical Advisory Board)
1p36 support group
Beckwith Wiedemann syndrome

Through these efforts I have helped develop several management guidelines including most recently guidelines for:

Pediatric Fabry disease

Hopkin RJ, Jefferies JL, Laney DA, Lawson VH, Mauer M, Taylor MR, Wilcox WR
Fabry Pediatric Expert Panel. The management and treatment of children with Fabry disease: A United States-based perspective. Mol Genet Metab. 2016 117(2):104-13 PMID: 26546059

Adult Fabry disease

Ortiz A, Germain DP, Desnick RJ, Politei J, Mauer M, Burlina A, Eng C, **Hopkin RJ**, Laney D, Linhart A, Waldek S, Wallace E, Weidemann F, Wilcox WR. Fabry disease revisited: Management and treatment recommendations for adult patients. Mol Genet Metab. 123(4):416-427. Epub 2018 PMID: 29530533

Neurofibromatosis type 1

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Miller DT, Freedenberg D, Schorry E, Ullrich NJ, Viskochil D, Korf BR; COUNCIL ON GENETICS; AMERICAN COLLEGE OF MEDICAL GENETICS AND GENOMICS. Collaborators (11) Chen E, Trotter TL, Berry SA, Burke LW, Geleske TA, Hamid R, **Hopkin RJ**, Introne WJ, Lyons MJ, Scheuerle AE, Stoler JM. Health Supervision for Children With Neurofibromatosis Type 1. *Pediatrics*. 2019 143(5). PMID: 31010905 (AAP treatment guidelines)

Down Syndrome

Bull MJ, Trotter T, Santoro SL, Christensen C, Grout RW; COUNCIL ON GENETICS, Burke LW, Berry SA, Geleske TA, Holm I, Hopkin RJ, Introne WJ, Lyons MJ, Monteil DC, Scheuerle A, Stoler JM, Vergano SA, Chen E, Hamid R, Downs SM, Grout RW, Cunniff C, Parisi MA, Ralston SJ, Scott JA, Shapira SK, Spire P. Health Supervision for Children and Adolescents With Down Syndrome. *Pediatrics*. 2022 149(5):e2022057010. PMID: 35490285

Congenital hypothyroidism

Rose SR, Wassner AJ, Wintergerst KA, Yayah-Jones NH, Hopkin RJ, Chuang J, Smith JR, Abell K, LaFranchi SH; SECTION ON ENDOCRINOLOGY EXECUTIVE COMMITTEE; COUNCIL ON GENETICS EXECUTIVE COMMITTEE. Congenital Hypothyroidism: Screening and Management. *Pediatrics*. 2023 1;151(1):e2022060420. PMID: 36827521

Rose SR, Wassner AJ, Wintergerst KA, Yayah-Jones NH, Hopkin RJ, Chuang J, Smith JR, Abell K, LaFranchi SH; SECTION ON ENDOCRINOLOGY EXECUTIVE COMMITTEE; COUNCIL ON GENETICS EXECUTIVE COMMITTEE. Congenital Hypothyroidism: Screening and Management. *Pediatrics*. 2023 1;151(1):e2022060419. PMID: 36827523

7. Research and Scholarly Activities

My research interests have been highly variable being generally related to both my educational commitments and my clinical activities. I have published on both well established and very rare genetic conditions. This has included descriptions of conditions, identification of the genetic basis, and natural history studies of certain conditions. The principle applied to my clinical research has been the goal of improving functional outcomes through application of what is known about the genetic causes of disease. Most of these kinds of studies have been done in part to support or update protocols related to the clinics I work or has been part of mentoring residents in early development of their chosen career interests. I have also done some research involving educational training needs related to medical genetics. This is directly related to the needs of our training program and how to have success in our genetic training programs (Genetic counseling, Nursing genetics, Medical students, and Genetic residency training). These pragmatic projects have generally been done without funding but have been important in the growth and development of the clinical services and training programs.

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Most of the funded research I have done is related to care for lysosomal diseases. I have been involved in several registries sponsored by pharmaceutical companies to fulfill their post marketing obligations. This provides an essential opportunity to improve use of the available treatments and increase the understanding of the long-term outcomes for progressive disease. I have also been an investigator on several clinical trials for enzyme replacement therapies, to chaperone drugs that can be used orally, and more recently application of gene therapy.

I am also interested in reapplication of known medications for use in treatment of rare genetic syndromes for example MEK inhibitors for treatment of neurofibromatosis type 1 or CBD derived medications for appetite suppression for Prader-Willi syndrome.

Grants and Contracts

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

ASPIRE Safety, Pharmacokinetics, Pharmacodynamics, and Efficacy of Migalastat in Pediatric Subjects with Fabry disease and amenable mutations (Aged 12 to <18 Years) sponsored by Amicus 5 patients enrolled

Type: Industry sponsored

Agency Amicus

Period 2018-2024

5 enrolled all have continued into extension phase

Role: Local PI

Time: 3%

Start-up: \$23,250 Per patient: \$21,186.90 per year (this study is nearing completion)

[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]




[REDACTED]

[REDACTED]

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Projects being considered or in development:

Follow Me Fabry Registry	Amicus	Start-Up
		

Publications

Original research publications (peer-reviewed)

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10. Stanek J, de Courten-Myers G, Spaulding AG, Strub W, **Hopkin RJ**. Case of complex craniofacial anomalies, bilateral nasal proboscides, palatal pituitary, upper limbs reduction, and amnion rupture sequence: disorganization phenotype? *Pediatr and Devl Pathol* 2001; 4:192-202 PMID: 11178637
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13. Howell KA, Huelsman KM, Everett JN, **Hopkin RJ**. Breast cancer genetics education for college women: an evaluation of approaches. *J Cancer Educ* 2002; 17: 74-77 PMID: 12092856
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13. Kishnani PS, Byrne BJ, Claeys KG, Díaz-Manera J, Dimachkie MM, Kushlaf H, Mozaffar T, Roberts M, Schoser B, Hummel N, Kopiec A, Holdbrook F, Shohet S, Toscano A; PROPEL Study Group (including **Hopkin R**). Switching treatment to cipaglucosidase alfa plus miglustat positively affects patient-reported outcome measures in patients with late-onset Pompe disease. *J Patient Rep Outcomes*. 2024 8(1):132. PMID: 39535661

Books, chapters, invited reviews and other publications (peer reviewed and non-peer-reviewed)

1. Klein SF, **Hopkin RJ**, Cohen M: Case Report: Infant scurvy. *Phoenix Children's Hospital Pediatric Review*, 6(2); 26-30, 1995. (invited report)
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5. Bloom, D. A., Koo, H. P., Bergeson, P. S., Piatt, J. P., **Hopkin, R. J.**, Bailey R B, J.,Perea-Martinez, A. (2000). Reply to letters regarding circumcision editorial (multiple letters). *Clinical Pediatrics*, 39(2), 129-132. (published letter)
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8. Prows CA, **Hopkin RJ**. Pierre Robin Sequence. In: *NORD Guide to Rare Disorders*. Lippincot Williams & Wilkins. Philadelphia, PA. 235-36. 2003. (invited paper)
9. Grabowski GA, **Hopkin RJ**. Lysosomal storage diseases. in *Harrison's Principles of Internal Medicine*, 16e McGraw-Hill Professional. New York 2003 (chapter)
10. Tinkle BT, **Hopkin RJ**, Grabowski GA. Enzyme therapy in Fabry disease. *Today's Therapeutic Trends*. 22: 181-200. 2004. (invited paper)
11. Whelan AJ, Ball S, Best L, Best RG, Echiverri SC, Ganschow P, **Hopkin RJ**, Mayefsky J, Stallworth J. Genetic red flags: clues to thinking genetically in primary care practice. *Prim. Care* 31: 497-508, 2004. PMID: 15331244 (invited paper) PMID: 15331244
12. **Hopkin R**. Treatments now available for lysosomal storage diseases. *AAP News* pages 10-11. 2005. (invited article)
13. Cragun D, **Hopkin RJ**. Use of the term "Antley-Bixler syndrome": minimizing confusion. *Am. J. Hum. Genet.* 77:327-328. 2005. PMID: 16145814 (published letter)
14. Cragun D, **Hopkin RJ**. Cytochrome P450 Oxidoreductase Deficiency. In: *GeneReviews at GeneTests: Medical Genetics Information Resource* [database online]. copyright, University of Washington, Seattle, 1997-2005. Available at <http://www.genetests.org>. posted September 2005. (invited entry)
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17. Zarate YA, **Hopkin RJ**. Pediatric quality of life in Anderson - Fabry disease: a review. Current medical literature / Lysosomal storage diseases 7:8-15. 2007. (invited review)
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19. **Hopkin RJ**, Grabowski GA. Lysosomal storage diseases. in Harrison's Principles of Internal Medicine, 17e, pp 3452-3456. McGraw-Hill Medical. New York. 2008. (chapter revision and update)
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31. Idkowiak J, Cragun D, **Hopkin RJ**, Arlt W. Cytochrome P450 Oxidoreductase Deficiency. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, Bird TD, Ledbetter N, Mefford HC, Smith RJH, Stephens K, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2017. 2005 Sep 8 [updated 2017 Aug 3]. PMID: 20301592 (entry revision and update)
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34. 30. Chapman T, Santoro SL, **Hopkin RJ**. Chapter 30 Chromosomal and Genetic Syndromes. In Fundamental and Advanced Fetal Imaging ultrasound and MRI chapter 30 Beth M. Kline-Fath, Dorothy I. Bulas, Ray Bahado-Singh eds. Wolters Kluwer Health 2021 China (chapter)*
35. Bull MJ, Trotter T, Santoro SL, Christensen C, Grout RW; COUNCIL ON GENETICS, Burke LW, Berry SA, Geleske TA, Holm I, **Hopkin RJ**, Introne WJ, Lyons MJ, Monteil DC, Scheuerle A, Stoler JM, Vergano SA, Chen E, Hamid R, Downs SM, Grout RW, Cunniff C, Parisi MA, Ralston SJ, Scott JA, Shapira SK, Spire P. Health Supervision for Children and Adolescents With Down Syndrome. Pediatrics. 2022 149(5):e2022057010. PMID: 35490285
36. **Hopkin RJ**, Grabowski GA. Lysosomal Storage Diseases. In Harrison's Principles of Internal Medicine 21e Chapter 411 Pages **** McGraw Hill / Medical; 21st edition (March 28, 2022) (Chapter revision and update)
37. Trivedi VS, Magnusen AF, Rani R, Marsili L, Slavotinek AM, Prows DR, **Hopkin RJ**, McKay MA, Pandey MK. Targeting the Complement-Sphingolipid System in COVID-19 and Gaucher Diseases: Evidence for a New Treatment Strategy. Int J Mol Sci. 2022 Nov 18;23(22):14340. PMID: 36430817

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38. Vyoma Snehal Trivedi , Albert Frank Magnusen , Reena Rani , Luca Marsili , Anne Michele Slavotinek , Daniel Ray Prows , **Robert James Hopkin** , Mary Ashley McKay , Manoj Kumar Pandey. Complement–Sphingolipid System in COVID-19 and Gaucher Diseases. Scholarly Community Encyclopedia November 25, 2022. This entry is adapted from 10.3390/ijms232214340 <https://encyclopedia.pub/entry/36640>
39. Rose SR, Wassner AJ, Wintergerst KA, Yayah-Jones NH, **Hopkin RJ**, Chuang J, Smith JR, Abell K, LaFranchi SH; SECTION ON ENDOCRINOLOGY EXECUTIVE COMMITTEE; COUNCIL ON GENETICS EXECUTIVE COMMITTEE. Congenital Hypothyroidism: Screening and Management. Pediatrics. 2023 1;151(1):e2022060420. PMID: 36827521
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Quality review of publications

1. Prada CE, Rangwala FA, Martin LJ, Lovell AM, Saal HM, Schorry EK, **Hopkin RJ**. Pediatric Plexiform Neurofibromas: Impact on Morbidity and Mortality in Neurofibromatosis Type 1. J Pediatr. 2012; 160(3):461-7 PMID: 21996156
This project evaluated the longitudinal outcomes of plexiform neurofibromas for hundreds of patients and helped delineate the morbidity associated with these tumors. It has been a valuable resource as clinical trials have been planned and completed. Thus this work contributed to development of better treatment options for patients and their families.
I was the project mentor working closely with both Carlos Prada a resident at the time, and Fatima Rangwala an M.D. PhD student. I was involved in all aspects of the project.

Citations: Total 74; Past 5 years 49

2018 9

2019 8

2020 11

2021 16

2022 5

2. Weaver KN, Wang D, Cnota J, Gardner N, Stabley D, Sol-Church K, Gripp KW, Witte D, Bove KE, **Hopkin RJ**. Early-Lethal Costello syndrome due to rare HRAS tandem base substitution (c.35_36GC>AA; p.G12E) associated pulmonary vascular disease. Pediatr Dev Pathol. 2014 17(6):421-30 PMID: 25133308
This paper was a single case report in which we noted that RAS activation appeared to be a key driver for progressive cardiovascular deterioration. It lead to a series of clinical interventions that are now promising leads and nearly ready to support clinical trials for treatment of this lethal complication of RAS pathway disease. It has been a key focus for

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2 of our Pediatrics/Genetics residents including Dr. Weaver who is now a faculty member at Cincinnati Children's Hospital and has continued to pursue this. We have now been able to improve outcomes and save the lives of a small number of patients.

I was the primary mentor on this project and involved in all phases of its completion.

Citations: Total 4; in the past 5 years 3

2016 1

2019 1

2020 1

2022 1

3. Brazil A, Stanford K, Smolarek T, **Hopkin R**. Delineating the phenotype of 1p36 deletion in adolescents and adults. Am J Med Genet A. 2014 164(10):2496-503 PMID: 25044719

This paper was initiated at the request of the national support group for 1p36 deletion. It is now the best available reference for long term outcomes related to 1p36 deletion. The outcomes were substantially better than reflected in previous publications that focused on infancy and early childhood. The families have greatly appreciated the hope this research brought.

I was the mentor and chair for the project that was completed as a thesis project by Ashley Brazil who was a genetic counseling student at the time.

Citations: Total 9; Past 5 years 7

2018 1

2020 2

2021 3

2022 1

4. Santoro SL, Esbensen AJ, **Hopkin RJ**, Hendershot L, Hickey F, Patterson B. Contributions to Racial Disparity in Mortality among Children with Down Syndrome. J Pediatr. 2016 Jul; 174:240-246.e1. PMID: 26993266

This paper was one of 6 publications on Down by Dr. Santoro as part of her residency at CCHMC. For this paper we found no evidence of biologic drivers for discrepant outcomes, but many socioeconomic barriers to care that accounted for the differences in mortality and other severe morbidities. This is essential to address the underlying causes.

I was the primary mentor for Dr. Santoro and was involved in all phases of the research. This paper is an example of the importance of asking new questions even about well-established and studied conditions.

Citations: Total 5; Past 5 years 5

2020 1

2021 3

2022 1

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5. **Hopkin RJ**, Cabrera G, Charrow J, Lemay R, Martins AM, Mauer M, Ortiz A, Patel MR, Sims K, Waldek S, Warnock DG, Wilcox WR. Risk factors for severe clinical events in male and female patients with Fabry disease treated with agalsidase beta enzyme replacement therapy: Data from the Fabry Registry. *Mol Genet Metab.* 2016 119(1-2):151-9. PMID: 27510433

This paper evaluated the long term outcomes of patients treated for Fabry disease focusing on major clinical events such as renal failure, heart failure, stroke and death. It was done through the Fabry registry so included a large number of patients and data over several years. This was part of development of updated treatment guidelines that have since been published as well.

I was the lead author and worked on all phases of the project from initial idea through multiple approaches to data analysis and writing and revising the manuscript.

Citations: Total 34; Past 5 years 21

2018 3

2019 3

2020 8

2021 4

2022 3

6. **Hopkin RJ**, Jefferies JL, Laney DA, Lawson VH, Mauer M, Taylor MR, Wilcox WR Fabry Pediatric Expert Panel. The management and treatment of children with Fabry disease: A United States-based perspective. *Mol Genet Metab.* 2016 117(2):104-13 PMID: 26546059

This paper was written because it was evident that the guidelines and outcome measures recommended for adults with Fabry disease did not apply to children (no renal disease, or heart disease is expected but children do have pain, significant GI disturbance and other problems). It was driven by expert opinion at the time, but was written with the intent to follow a cohort of children and will be updated. It was the first guideline for management of Fabry disease in pediatric patients.

I was the lead author and helped organize and run the meetings in which the paper was drafted.

Citation: Total 41; Past 5 years 35

2018 9

2019 5

2020 11

2021 9

2022 1

7. Lombardo RC, Porollo A, Cnota JF, **Hopkin RJ**. Congenital heart disease and aortic arch variants associated with mutation in PHOX2B. *Genet Med.* 2018 20(12):1538-1543 PMID: 29543228

This paper was inspired by a resident noting that she had 2 patients with PHOX2B mutations with heart defects but that the literature did not mention that. We then reviewed all the cases of this rare disorder in the records at Cincinnati children's hospital

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and found that the incidence of heart malformations was substantially increased. This expanded the phenotype and increased the chance for optional management of this complex disorder.

I was the primary mentor for this project and guided Dr. Lombardo through all phases of the project from inception through publication.

Citations: Total 8; Past 5 years 8

2019 1

2020 2

2021 4

2022 1

8. Campion M, Goldgar C, **Hopkin RJ**, Prows CA, Dasgupta S. Genomic education for the next generation of health-care providers. *Genet Med*. 2019 21(11):2422-2430 Review. PMID: 31110330

This paper reviews the anticipated need for providers of genetic services including physicians, Genetic counselors, physician assistants, and various nursing roles.

The project started as an invited symposium at ACMG. I suggested the summary be drafted as a paper for publication and wrote the section on physicians and residency training and helped with revisions until publication

Citations: Total 33; Past 5 years 33

2019 3

2020 11

2021 15

2022 4

9. Lukacs M, Gilley J, Zhu Y, Orsomando G, Angeletti C, Liu J, Yang X, Park J, **Hopkin RJ**, Coleman MP, Zhai RG, Stottmann RW. Severe biallelic loss-of-function mutations in nicotinamide mononucleotide adenylyl transferase 2 (NMNAT2) in two fetuses with fetal akinesia deformation sequence. *Exp Neurol*. 2019 320:112961 PMID: 31136762

This report describes the first family with biallelic complete loss of function in NMNAT2. This is the first human disorder of Wallerian degeneration. It makes an important contribution to understanding of brain development. I was the clinician who recognized the uniqueness of the phenotype and requested whole exome sequence. I helped the family enroll in the research, and helped draft and edit the manuscript. The laboratory work was done in collaboration with Rolf Stottmann in Cincinnati and 2 outside research labs.

Citations: Total 23; Past 5 years 23

2019 2

2020 5

2021 13

2022 3

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10. Schulze KV, Szafranski P, Lesmana H, **Hopkin RJ**, Hamvas A, Wambach JA, Shinawi M, Zapata G, Carvalho CMB, Liu Q, Karolak JA, Lupski JR, Hanchard NA, Stankiewicz P. Novel parent-of-origin-specific differentially methylated loci on chromosome 16. Clin Epigenetics. 2019 Apr 8;11(1):60. PMID: 30961659

This paper is the first well documented evidence of imprinting associated with uniparental disomy 16. Dr. Lesmana and I had collected several patients with very similar phenotypes and UPD 16. We contacted a basic science lab and provided them with patient samples detailed clinical descriptions and our hypothesis that the phenotype was related to imprinting.

I was the main clinical and research mentor for Dr. Lesmana and was involved mainly in conception and clinical data collection for this work.

Citations: Total 8; Past 5 years 8

2020 1

2021 6

2022 1

Patents

None

Abstracts

1. **Hopkin RJ**, Schorry EK, Bofinger M, Milatovich T, Stern HJ, Saal HM: New insights into the phenotypes of 6q deletions. The Am J Hum Genet, 57(4): A116, October 1995. Presented as a poster at the American Society of Human Genetics Annual Meeting in Minneapolis, MN (International)
2. Hoechstetter LB, Schorry EK, **Hopkin RJ**, McKinivan CE: Leber's congenital amaurosis in an Amish family, March of Dimes Clinical Genetics Conference, Los Angeles, CA, 1995.
3. **Hopkin RJ**, Cotton RT, Saal HM: A new condition with short stature, progressive tracheolaryngeal stenosis and dysmorphic facies, March of Dimes Clinical Genetics Conference, Los Angeles, CA, 1995. Poster presentation (National)
4. Saal HM, **Hopkin RJ**: A New dominant syndrome with microphthalmia, cataracts, and cleft palate, David W. Smith Malformation and Morphogenesis Workshop, Helena, MT, 1995.
5. Saal HM, Bofinger M, **Hopkin RJ**, New clinical findings in the velo-cardio-facial syndrome, Platform presentation at the American Cleft Palate-Craniofacial Annual Meeting, April 24, 1996.
6. Saal HM, Bofinger M, **Hopkin RJ**: Renal Agenesis and other renal anomalies associated with the velo-cardio-facial syndrome and deletion 22q11.2, David W. Smith Malformation and Morphogenesis Workshop, Lake Arrowhead, CA, 1996.

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7. **Hopkin RJ**, Schorry EK, Bofinger M, Saal HM: Velocardiofacial syndrome in the newborn and infant, Platform presentation, American Society of Human Genetics Annual Meeting, San Francisco, CA, 1996. (International)
8. **Hopkin RJ**, Schorry EK, Bofinger M, Saal HM: Velocardiofacial syndrome in the newborn and infant, Am J Hum Genet, 59(4):A20, 1996.
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10. **Hopkin RJ**, Cotton R, Saal HM: Progressive tracheolaryngeal stenosis with short stature and arthropathy, David W. Smith Malformation and Morphogenesis Workshop, Litchfield Beach SC, 1997. (International)
11. Saal HM, Ringhand T, Prows CA, **Hopkin RJ**. Genetic etiologies of velopharyngeal insufficiency. Poster presentation, American Society of Human Genetics Annual Meeting, Baltimore MD, 1997.
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13. Schorry EK, **Hopkin RJ**, Loggie J. Hypertension in neurofibromatosis-1: possible racial differences. Am J Hum Genet, 63(4): A663, 1998.
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15. **Hopkin RJ**, Walker M, Stanek J. Familial posterior urethral valves as a cause for prune-belly. Poster presentation for the American College of Medical Genetics annual meeting Miami Florida, March 19-21, 1999 (National)
16. **Hopkin RJ**, West CE. Robin sequence with distichiasis: A new dominant syndrome. Platform presentation, Tristate Dysmorphology Conference, Lexington KY, May 21, 1999 (Regional)
17. **Hopkin RJ**, West CE. Robin sequence with distichiasis: a new dominant syndrome. Am J Hum Genet 65:A826, 1999.
18. **Hopkin RJ**, West CE. Robin sequence with distichiasis: a new dominant syndrome. Poster presentation at the American society of Human Genetics annual meeting San Francisco California, Oct. 19-23, 1999 (international)
19. **Hopkin RJ**, Huelsman K, Johnson J, Korfhagen T. A protocol for IRB oversight of clinically indicated research testing. Am J Hum Genet 67: A273, 2000.

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20. **Hopkin RJ**, Huelsman K, Johnson J, Korfhagen T. A protocol for IRB oversight of clinically indicated research testing. Platform presentation at the American Society of Human Genetics Annual Meeting Philadelphia Pennsylvania, Oct. 3-7, 2000 (international)
21. Zhao H, Rope A, Blough RI, Saal HM, **Hopkin RJ**. Expanded phenotype of partial trisomy 11q. Am J Hum Genet 67: A558, 2000.
22. Zhao H, Rope A, Blough RI, Saal HM, **Hopkin RJ**. Expanded phenotype of partial trisomy 11q. Poster presentation, American Society of Human Genetics Annual Meeting Philadelphia Pennsylvania, Oct. 3-7, 2000 (international)
23. Johnson JA, Blough RI, Jayne CH, Schorry EK, **Hopkin RJ**, Saal HM. Terminal deletion of chromosome 1p36: new insights into clinical features and medical management. Am J Hum Genet 67:A643, 2000.
24. Johnson JA, Blough RI, Jayne CH, Schorry EK, **Hopkin RJ**, Saal HM. Terminal deletion of chromosome 1p36: new insights into clinical features and medical management Poster presentation, American Society of Human Genetics Annual Meeting Philadelphia Pennsylvania, Oct. 3-7, 2000 (international)
25. Walker ME, **Hopkin RJ**, Saal HM. Perinatal hospice: recent experience with prenatal diagnosis of lethal abnormalities. J Genet Counseling 9:474-475.
26. Walker ME, **Hopkin RJ**, Saal HM. Perinatal hospice: recent experience with prenatal diagnosis of lethal abnormalities National Society of Genetic Counselors Annual meeting Savannah Georgia, November 2000 (International)
27. Hepler G, Rice C, **Hopkin R**, Huelsman K, Warren N. Genetic counseling for occupational hazards. J Genet Counseling 9:517-518.
28. Hepler G, Rice C, **Hopkin R**, Huelsman K, Warren N. Genetic counseling for occupational hazards, National Society of Genetic Counselors Annual Meeting Savannah Georgia, November 2000 (International)
29. Zhao H, **Hopkin RJ**, Saal HM. Atypical presentation of Bloom syndrome. Am J Hum Genet 69:A635, 2001
30. Zhao H, **Hopkin RJ**, Saal HM. Atypical presentation of Bloom syndrome. Poster presentation, American Society of Human Genetics Annual Meeting San Diego California, Oct. 13-16, 2001 (International)
31. **Hopkin RJ**, Walker ME, Saal HM, Schorry EK, Tucker L. Perinatal hospice: an important option for families continuing pregnancies following the diagnosis of lethal conditions. Am J Hum Genet 69:A2870, 2001

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32. **Hopkin RJ**, Walker ME, Saal HM, Schorry EK, Tucker L. Perinatal hospice: an important option for families continuing pregnancies following the diagnosis of lethal conditions. Poster presentation, American Society of Human Genetics Annual Meeting San Diego California, Oct. 13-16, 2001 (International)
33. Howell K, Huelsman K, Everett J, **Hopkin R**. Breast cancer genetics education for college women: an evaluation of approaches. J Genet Counseling 10:443-444
34. Wille M, Walker M, **Hopkin R**, Zins J, Noll R. An assessment of genetic counseling needs and concerns of pediatric cancer survivors. J Genet Counseling 10:461-462
35. Rope AF, Benson DW, Howell KA, Andelfinger GU, **Hopkin RJ**. The variable phenotype of velocardiofacial syndrome in an extended family, American College of Medical Genetics Annual meeting New Orleans, Louisiana Mar 2002 (International)
36. Rope AF, Benson DW, Howell KA, Andelfinger GU, **Hopkin RJ**. The variable phenotype of velocardiofacial syndrome in an extended family. Genetics in Medicine 4(3) A94, 2002
37. Tinkle BT, Walker ME, Saal HM, **Hopkin RJ**. Unexpected survival in a case of prenatally diagnosed non-mosaic trisomy 22, American College of Medical Genetics Annual Meeting, New Orleans, Louisiana Mar 2002 (International)
38. Tinkle BT, Walker ME, Saal HM, **Hopkin RJ**. Unexpected survival in a case of prenatally diagnosed non-mosaic trisomy 22. Genetics in Medicine 4(3) A97, 2002
39. Rope AF, Schorry EK, **Hopkin RJ**, Saal HM. DiGeorge anomaly in the absence of deletion 22q11.2 brief presentation at the 23rd Annual David Smith workshop on Malformations and Morphogenesis. Greenville South Carolina Aug 2002 (platform)
40. **Hopkin RJ**, Zhao H, Gorlin RJ. Ermine phenotype: further characterization of neurologic and pigmentary features. Platform presentation at the 23rd Annual David Smith workshop on Malformations and Morphogenesis. Greenville South Carolina Aug 2002 (platform)
41. **Hopkin RJ**, Schorry Ek. Muscular hypertrophy and mental retardation. A provisionally unique syndrome or first female case of Myhre syndrome. the 23rd Annual David Smith workshop on Malformations and Morphogenesis. Greenville South Carolina Aug 2002 (platform)
42. Webb T, **Hopkin RJ**. Genetics for primary care. SGIM Midwestern region Annual Meeting Chicago IL, Sept 2002.
43. **Hopkin RJ**, Samaha FJ, Zhao H, Bailey L, Grabowski GA. Neurologic complications of female and male patients with Fabry disease. Poster presentation at the American Society of Human Genetics Annual Meeting, Baltimore MD Oct 2002 Also published abstract in the Am J Human Genet.

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44. Rope AF, Schorry EK, **Hopkin RJ**, Saal HM. DiGeorge anomaly in the absence of deletion 22q11.2. Poster presentation at the American Society of Human Genetics Annual Meeting, Baltimore MD Oct 2002 Also published abstract in the Am J Human Genet.
45. **Hopkin RJ**, Samaha FJ, Zhao H, Bailey L, Grabowski GA. Neurologic complications of female and male patients with Fabry disease. Platform presentation at the Annual World Symposium on Lysosomal Storage Diseases, Baltimore MD Oct 2002
46. Prows CA, Hetteberg C, **Hopkin RJ**, Latta KK, Powers S. Development of a web ased genetics institute for nursing faculty platform presentation at the ISONG Annual Meeting Baltimore MD, Oct 2002
47. Rope AF, **Hopkin RJ**, Saal HM. Evaluation of infants with cardiovascular malformations for recognizable etiologies. Poster presentation at the David Smith meeting in Vancouver British Columbia 2003.
48. Saal HM, Schorry EK, **Hopkin RJ**. Nasal speech and velopharyngeal dysfunction: a neglected feature of neurofibromatosis-1. Poster presentation at the David Smith meeting in Vancouver British Columbia 2003.
49. **Hopkin RJ**, Madden C, Halsted M, Choo D, Greinwald J, Benton C. Inner ear anomalies are common in Waardenburg syndrome. Poster presentation at the David Smith meeting in Vancouver British Columbia 2003.
50. **Hopkin RJ**, Mulrooney NP, Trumpy S. Undetectable unconjugated estriol associated with Antley-Bixler syndrome: further evidence for abnormal steroidogenesis. Am J Hum Genet 73:A2513 2003 Also poster presentation at the American Society of Human Genetics meeting in Los Angeles Nov. 2003.
51. Eng, CM, Banikazemi M, Barranger J, Charrow J, Clark L, Bushinsky D, **Hopkin R**, Pastores G, Scott CR, Sims K, Wilcox W. Fabry disease: Delineating the natural history of the disorder through the Fabry Registry. Am J Hum Genet 73:A1657 2003 Also poster presentation at the American Society of Human Genetics meeting in Los Angeles Nov. 2003.
52. Charrow J, Banikazemi M, Barranger J, Clark L, Eng CM, **Hopkin R**, Pastores G, Scott CR, Sims K, Wilcox W. Understanding the natural history of Fabry disease: The Fabry registry. Abstract and poster at the Pediatric Academic Societies meeting 2004.
53. Y. Tang, M. Schapiro, D. Franz, B. Patterson, F. Hickey, E.K. Schorry, **R.J. Hopkin**, M. Wylie, T. Narayan, A. Lu, R. Ran, T.A. Glauser, D.L. Gilbert, A.D. Hershey, F.R. Sharp. Blood expression profiles using microarrays for tuberous sclerosis complex 2, neurofibromatosis type 1 and Down. Society For Neuroscience Meeting at San Diego 2004

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54. Shooner KA, Rope AF, **Hopkin RJ**, Andelfinger GU, Benson DW. Reduced prevalence of cardiovascular malformations hinders detection in two large families with deletion 22q11.2 syndrome NSGC Annual meeting 2004.
55. Multhaupt T, Lovell A, Mills L, **Hopkin R**. Genetic Health Care Professional's Practice of Testing Adolescents for Carrier Status. NSGC annual meeting 2004.
56. Multhaupt T, Lovell A, Mills L, **Hopkin R**. Attitudes Regarding Testing Adolescents for Carrier Status. ASHG Annual Meeting Toronto Canada Oct 2004.
57. **Hopkin R**, Jansen N, Bailey L, Yi M. Decreased Quality of Life in Women With Fabry Disease. ASHG Annual Meeting Toronto Canada Oct 2004
58. **Hopkin RJ**, Arlt W, Cragun D, Kelley RI, Shackleton C. Abnormal steroidogenesis, deficiency of lanosterol 14-alpha-demethylase, and mutations in CPR in a patient with Antley-Bixler syndrome. David Smith meeting Utah Aug 2004 (internatioanal)
59. Moretti P, Peters S, Hyland K, Bottiglieri T, **Hopkin R**, Peach E, Roa B, Bacino C, Scaglia F. Autism spectrum manifestations in cerebral folate deficiency. ASHG Annual Meeting Toronto Canada Oct 2004 (international)
60. Tinkle BT, Bove KE, Hoffman I, Wood RE, **Hopkin RJ**. A case of geleophysic dysplasia: a lysosomal storage disease? WORLD Lysosomal Disease Research Network Symposium. Minneapolis, MN May 2004 (international)
61. Tinkle BT, Bove K, Hoffman I, Wood RE, **Hopkin RJ**. Geleophysic dysplasia: case report and evidence against lysosomal storage. David W. Smith 25th Annual Workshop on Malformations and Morphogenesis. Wasatch Mountains, Utah August 2004 (international)
62. **Hopkin RJ**. Fabry disease in childhood and adolescents. LSD Registries Conference Washington DC May 2004 (National)
63. Rope A, Saal HM, **Hopkin RJ**. The DiGeorge anomaly in the absence of deletion 22q11.2. The Irish and American Paediatric Society meeting Westport, Co. Mayo Ireland September 2004 (international)
64. White DR, Giambra BK, **Hopkin RJ**, Daines CL, Rutter MJ. Aspiration in children with CHARGE association. SENTAC Toronto Canada December 2004 (International)
65. Clarke LA, Barranger J, **Hopkin R**, Eng CM, Pastores G, Scott CR, Sims K, Wilcox W. Fabry disease presenting in the pediatric age group: clinical and ethical concerns. ACMG Dallas Texas March 2005 (International)
66. Clarke LA, Barranger J, **Hopkin R**, Eng CM, Pastores G, Scott CR, Sims K, Wilcox W. Fabry disease presenting in the pediatric age group: clinical and ethical concerns. PAS 2005 (International)

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67. **Hopkin RJ.** Treatment decisions in MPS I case discussion. 2nd Annual MPS I Symposium Phoenix AZ. May 20, 2005 (international)
68. Kogan J, Zenker M, Vandevoorde R, **Hopkin RJ.** Prolonged survival in Pierson syndrome. David W. Smith 26th Annual Workshop on Malformations and Morphogenesis. Iowa City , Iowa August 2005 (international)
69. Saal HM, Bao L, Schorry EK, **Hopkin RJ,** Leslie ND, Smolarek T. Paucity of primary identification of new cryptic subtelomere rearrangements with subtelomere FISH: a three year retrospective analysis. David W. Smith 26th Annual Workshop on Malformations and Morphogenesis. Iowa City , Iowa August 2005 (international)
70. Rope A, Saal HM, **Hopkin RJ.** An attempt at guidelines for FISH 22q11.2 derived from 6 years of testing experience. David W. Smith 26th Annual Workshop on Malformations and Morphogenesis. Iowa City , Iowa August 2005 (international)
71. Burrow A, **Hopkin R,** Bove K, Miles L, Wong B, Choudhary A, Bali D, Li SC, Chen YT. A mild congenital hypotonia and myopathy of glycogen storage disease type IV. David W. Smith 26th Annual Workshop on Malformations and Morphogenesis. Iowa City, Iowa August 2005 (International)
72. Zhao H, Saal HM, **Hopkin RJ.** Major malformations in Bloom syndrome. David W. Smith 26th Annual Workshop on Malformations and Morphogenesis. Iowa City, Iowa August 2005 (International)
73. Scaglia F, Moretti P, Peters S, Del Gaudio D, Hyland K, Bottiglieri T, **Hopkin R,** Peach E, Roa B, Bacino C, Clinical and genetic characterization of central nervous system folate deficiency. ASHG annual meeting Salt Lake City Utah October 2005 (International)
74. Reiter-Purtill J, Schorry EK, **Hopkin RJ,** Vannatta K, Lovell A, Gerhardt C, Moore B, Noll RB. Peer Relationships in neurofibromatosis 1. ASHG annual meeting Salt Lake City Utah October 2005 (International)
75. **Hopkin RJ,** White DR, Giambra BK, Daines CL, Rutter MJ. Aspiration and airway obstruction in CHARGE syndrome. ASHG annual meeting Salt Lake City Utah October 2005 (International)
76. Saal HM, Bao L, Schorry EK, **Hopkin RJ,** Leslie ND, Smolarek TA. Paucity of primary identification of new cryptic subtelomere rearrangements with subtelomere FISH: a three year retrospective analysis. ASHG annual meeting Salt Lake City Utah October 2005 (International)
77. Walker ME, Schorry EK, Bove KE, Das S, **Hopkin RJ,** Wong BL. A novel MTM1 gene mutation in an infant with X-linked myotubular myopathy and bladder exstrophy. ACMG annual meeting San Diego CA March 2006 (International)

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78. **Hopkin RJ**, Cragun D. Craniosynostosis as a new feature in van den Ende-Gupta syndrome. ACMG annual meeting San Diego CA March 2006 (International)
79. **Hopkin RJ**. Workshop Session: Fabry: Management of Early Disease Symptoms among Patients with Fabry Disease. 10th Annual LSD registries meeting Orlando Florida May 2006 (International)
80. Burrow TA, Walker M, **Hopkin RJ**. Milroy disease: prenatal diagnosis and phenotype variability in a family. David W. Smith 27 Annual Workshop on Malformations and Morphogenesis. Lake Arrowhead, CA September 2006 (International)
81. Saal HM, Kline-Fath B, Crombleholme T, Bender P, Rothchild D, Peach E, Elluru R, Willging JP, Gordon C, **Hopkin RJ**. The role of fetal MRI for diagnosis and management of fetal micrognathia and Pierre Robin sequence David W. Smith 27 Annual Workshop on Malformations and Morphogenesis. Lake Arrowhead, CA September 2006 (International)
82. **Hopkin RJ**, Saal HM, Rutter MJ, Hubbell R, Cotton R, Lindor MN, Holmes L, Lin AE. LAPS syndrome: 4 additional patients with emphasis on major morbidity and life threatening complications. David W. Smith 27 Annual Workshop on Malformations and Morphogenesis. Lake Arrowhead, CA September 2006 (International)
83. Burrow TA, Walker M, **Hopkin RJ**: Milroy disease: Prenatal diagnosis and phenotypic variability in a family. 27th Annual D.W. Smith Workshop on Malformations and Morphogenesis. September, 2006. Poster presentation
84. Burrow TA, Walker M, **Hopkin RJ**: Milroy disease: Prenatal diagnosis and phenotypic variability in a family. 56th Annual Meeting of the American Society of Human Genetics. October, 2006. Poster presentation
85. Zarate YA, **Hopkin RJ**. Unusual presentation of linear nevus syndrome ASHG New Orleans October 2006 Poster presentation (International)
86. **R.J. Hopkin**, B. Kline-Fath, T. Crombleholme, P. Bender, D. Rothchild, E. Peach, R. Elluru, J.P Willging, C. Gordon, and H.M. Saal. Prenatal imaging for the diagnosis of Robin Sequence and associated anomalies. American College of Medical Genetics annual meeting Nashville TN March 2007 (international)
87. Cragun D, **Hopkin RJ**. A Mutation in SOS1 as a Cause of Enlarged Nerve Roots and Peripheral Neuropathy in Noonan Syndrome? American College of Medical Genetics annual meeting Nashville, TN March 2007 (international)
88. Burrow TA, Saal HM, **Hopkin RJ**: High Frequency of Central Nervous System Malformations Associated with Choanal Atresia. 57th Annual Meeting of the American Society of Human Genetics. October, 2007. Poster presentation.

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89. **Hopkin RJ**, Wood RE, Elluru RG. The respiratory phenotype in survivors with Campomelic dysplasia. David W. Smith 28 Annual Workshop on Malformations and Morphogenesis. Williamsburg VA August 2007 (International)
90. Zarate YA, **Hopkin RJ**. The genetic evaluation of macroglossia. David W. Smith 28 Annual Workshop on Malformations and Morphogenesis. Williamsburg VA August 2007 (International)
91. Burrow TA, Saal SM, **Hopkin RJ**. Choanal atresia: Thinking beyond CHARGE syndrome. David W. Smith 28 Annual Workshop on Malformations and Morphogenesis. Williamsburg VA August 2007 (International)
92. **Hopkin RJ**, Simms K. Pediatric Fabry disease: answering the unanswered questions. Lysosomal disease registries meeting Salt Lake City UT May 2007 (National)
93. Kogan JM, Smolarek TA, **Hopkin RJ**, Grabowski GA. Dissection of apparently balanced translocations using high density SNP arrays. ASHG San Diego CA Oct. 2007 (International)
94. Zarate YA, **Hopkin RJ**. The genetic evaluation of macroglossia. ASHG San Diego CA Oct. 2007 (International)
95. Burrow, T.A., Saal, H.M., **Hopkin, R.J.** High frequency of central nervous system malformations associated with choanal atresia. ASHG San Diego CA Oct. 2007 (International)
96. Zarate YA, Mena R, **Hopkin RJ**, Tinkle Brad, Steele P. Experience with Hemihypertrophy and Beckwith Wiedemann Syndrome Surveillance Protocol. Platform presentation at the American Collage of Medical Genetics Meeting. March 2008.
97. **R.J. Hopkin**, C.V.A. Guimaraes, L.E. Linam, B.M. Kline-Fath, L.F. Donnelly, F.Y. Lim, M.A. Calvo-Garcia, E.I. Rubio, J.C. Livingston, T. M. Crombleholme. Congenital High Airway Obstruction Sequence (CHAOS) a recognizable malformation sequence with potential interventions based on the pathogenic mechanism. David W. Smith 29 Annual Workshop on Malformations and Morphogenesis. Mount Tremblant Canada 2008 (International)
98. MB Rieley, BM Kline-Fath, **RJ Hopkin**. Aqueductal Stenosis: Can fetal MRI findings help predict developmental outcome? David W. Smith 29 Annual Workshop on Malformations and Morphogenesis. Mount Tremblant Canada 2008 (International)
99. Myles Reid, D., Chong, K., Kolomietz, E., **Hopkin R**, Bedard, A. and Kogan, J. Prenatal diagnosis of marker chromosome 4: a report of two cases with outcomes. ASHG Philadelphia PA. Nov 2008.
100. Glorieux, FH; Bishop, N; Bober, M; Brain, CE; Devogelaer, J; Fekete, G; Forin, V; **Hopkin, RJ**; Kaitila, I; Lee, B; Lorenc, R; Mahan, JD; McCallister, JA; Pettifor, JM; Plotkin, H; Rauch, F; Salusky, IB; Shaw, N; Showalter, L; Steelman, JW; Steiner, R; Tan, M; Zhou, W; Bucci-Rechtweg, C. (2008). Intravenous zoledronic acid (ZOL) compared to IV pamidronate

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(PAM) in children with severe osteogenesis imperfecta (OI). CALCIFIED TISSUE INTERNATIONAL, 82, S85.

101. Spaeth CG, Rubio E, **Hopkin RJ**. Utility of Fetal MRI in the Diagnosis and Management over a Spectrum of Genetic Syndromes: Case Series, as a Contributed Paper at the NSGC 28th Annual Education Conference in Atlanta, Georgia 2009

102. **Hopkin RJ**, Bissler J, Banikazemi M, Clarke L, Eng CM, Germain DP, Lemay R, Tylki-Szymanska A, Wilcox WR. Substantial Signs and Symptoms of Fabry Disease Among Children: Natural History Data from 352 Pediatric Patients in the Fabry Registry European Round Table on Fabry disease, 2009. (International)

103. Prada CE, Zarate YA, Schorry EK, **Hopkin RJ**. Severe Presentation of Neurofibromatosis and Noonan Syndrome. Poster American Collage of Medical Genetics Meeting. March, 2009.

104. **Hopkin RJ**, Prada C, Lovell A, Schorry E, Cragun D. Neurofibromatosis and Noonan syndrome: on the overlapping phenotypes. David W. Smith 30th Annual Workshop on Malformations and Morphogenesis. Philadelphia, PA, 2009.

105. Prada C, **Hopkin RJ**. Severe prenatal cervical scoliosis in the fetus: prenatal diagnosis, prognosis and outcome. David W. Smith 30th Annual Workshop on Malformations and Morphogenesis. Philadelphia, PA, 2009.

106. **Hopkin RJ**. Fabry disease. Genzyme Registries Southeast Regional Meeting. Baltimore, MD, 2009.

107. 17p deletion LIS1 intact with Debi Cragun 2009

108. Watt T, Feldt-Rasmussen U, Burlina A, Cazzorla C, Schönfeld D, Banikazemi M, **Hopkin RJ**, Martins A, Sims K, Beitner-Johnson D, O'Brien F. Agalsidase Beta Treatment Improves Quality of Life in Patients with Fabry Disease: Findings from the Fabry Registry. Poster American College of Medical Genetics annual meeting, March 2010.

109. **Hopkin RJ**, Diegmueeller J, Leslie N, Ruschman J, Saal HM, Grabowski GA. Achieving financial independence for clinical genetic services: Is it truly possible? Poster American College of Medical Genetics annual meeting, March 2010.

110. Carlos Prada, Fatima Rangwala, Elizabeth Schorry, Anne Lovell, Howard Saal, and **Robert J. Hopkin**. Morbidity Associated with Pediatric Plexiform Neurofibromas. Platform presentation American College of Medical Genetics annual meeting, March 2010.

111. **Robert J. Hopkin**, Elizabeth Hopkin, Brad Tinkle, Katie Wusik. Dysmorphic syndromes in adults presenting for genetic services. Platform presentation David W. Smith 31st annual Workshop on Malformations and Morphogenesis Alderbrook Resort, Union, Washington 2010

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112. Ashley Parrott, Melanie Myers, **Robert Hopkin**, John Lynch. Media Coverage of Direct-to-Consumer Genetic Testing. NSGC annual meeting 2010
113. **Robert J. Hopkin**, Maryam Banikazemi, Dominique P. Germain, Michael Mauer, Anna Tylki-Szymanska, David G. Warnock, William A. Wilcox. Guidelines for the evaluation and management of children with Fabry disease. Poster ASHG annual meeting Washington DC 2010
114. C. Prada, F. Rangwala, A. Gallas, E. Sites, A. Lovell, E. Schorry, H. Saal, **R. Hopkin**. Plexiform Neurofibromas Morbidity in a Large Cohort of Pediatric Patients. Platform presentation ASHG annual meeting Washington DC USA 2010
115. Elizabeth A. Sellars, Nancy D. Leslie, **Robert J. Hopkin**. Rapid Treatment Response for Severe MTHFR Deficiency. Poster Annual Clinical Genetics Meeting - American College of Medical Genetics. March 16–20, 2011 in Vancouver, BC, Canada
116. E.K. Schorry, J.K. George-Abraham, M.B. Rieley, D.A. Stevenson, D.H. Viskochil, **R.J. Hopkin**, L. J. Martin, H.J. Kalkwarf, A.M. Stevens, S. Allen. Differences in Fractures and Activity in Children with NF1. Poster ASHG annual meeting Montreal Canada 2011
117. Emily King, BJ Leech, K Stanford, HM Saal, J James, SR Callahan, S Geraghty, I Sagesser, and **RJ Hopkin**. Increased Medical Interventions in Children with 22q11.2 Deletion Syndrome (Velocardiofacial Syndrome). NSGC meeting 2011
118. Emily King, BJ Leech, K Stanford, HM Saal, J James, SR Callahan, S Geraghty, I Sagesser, and **RJ Hopkin**. Increased Medical Interventions in Children with 22q11.2 Deletion Syndrome (Velocardiofacial Syndrome). Poster ASHG annual meeting Montreal Canada 2011
119. K. J. Patek, B. M. Kline-Fath, V. V. Pilipenko, C. G. Spaeth, Crombleholme T, **R. J. Hopkin**. Posterior fossa anomalies diagnosed with fetal MRI: Associated anomalies and neurodevelopmental outcomes. Platform presentation ASHG annual meeting Montreal Canada 2011
120. K. J. Patek, B. M. Kline-Fath, V. V. Pilipenko, C. G. Spaeth, Crombleholme T, **R. J. Hopkin**. Posterior fossa anomalies diagnosed with fetal MRI: Associated anomalies and neurodevelopmental outcomes. Poster NSGC 2011 won award for outstanding poster with a cash prize (this is not limited to trainee presentations).
121. Christine G Spaeth, Diana L. Smith, **Robert J Hopkin**. When Identical Isn't the Same: Curious Cases of Discordant Twins. NSGC 2011
122. Carlos Prada, MD, Nicki Smith, Anne Lovell, CNP, **Robert Hopkin**, MD, Elizabeth Schorry, MD, Howard Saal, M.D. Optic Pathway Gliomas: Case series. Poster Children's Tumor Foundation National meeting 2011

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123. Elizabeth A. Sellars, Katie Wusik, Nicole Weaver, **Robert J. Hopkin**. Variable presentation between a mother and fetus affected with Goltz syndrome. Poster ACMG meeting 2012
124. Angela Lin, Sulagna Saitta, Tara Wenger, Rosemarie Smith, Michael Epstein, Mark Alexander, Karen Gripp, Elizabeth Hopkins, Jaya Ganesh, Jennifer Kalish, Mark Levin, Carlos Prada, **Robert Hopkin**, Elaine Zackai. Non-reentrant tachycardia in dysmorphic infants suggests RASopathy: ACMG meeting 2012.
125. Carlos E. Prada, MD, Nicki R. Smith, BS, Lisa J. Martin, PhD, Anne M. Lovell, CNP, **Robert J. Hopkin**, MD, Elizabeth K. Schorry, MD, and Howard M. Saal, MD. Magnetic Resonance Imaging Screening for Optic Pathway Gliomas in Neurofibromatosis type 1. ACMG meeting 2012
126. **Robert J. Hopkin**, Michael Mauer, Roberta Lemay, Jörg Strotmann, Katherine B. Sims. Early initiation of agalsidase beta treatment is associated with fewer clinical events: data from the Fabry Registry. WORLD lysosomal Disease Meeting San Diego CA 2012
127. Prada CE, Cecil K, Wehmeyer C, Berry L, Bailey L, **Hopkin RJ**, Leslie ND, Grabowski GA. (2012). Developing Brain Imaging Markers of Treatment Response and Progression in Mucopolysaccharidosis Type II. WORLD meeting, Feb 2012. Mol Gen Metab, 105(2):s53-s54 .
128. Smith DL, **Hopkin R**, Bous SM, Kline-Fath, B. Recurrent holoprosencephaly of unknown etiology: the importance of pursuing genetic diagnosis and implications for family counseling ISPD meeting 2012
129. Korf B, et al. (including **Hopkin RJ**). Natural History of Plexiform Neurofibromas in NF1. Children's Tumor Foundation National meeting 2012
130. K. N. Weaver, M. EL-Hallak, M. Keddache, C. Hankin, S. Das, **R. Hopkin**. A unique presentation of Keutel syndrome illustrating similarities with relapsing polychondritis David W. Smith 33rd annual Workshop on Malformations and Morphogenesis Poster 2012
131. **Robert J. Hopkin**, Carlos E. Prada, Pinar Bayrack-Toydemir, Lindor, Comier-Dair. SMAD4opathies: Myhre syndrome and LAPS syndrome. David W. Smith 33rd annual Workshop on Malformations and Morphogenesis Poster 2012
132. Howard M. Saal, Patricia L Bender, **Robert J. Hopkin**. Pierre Robin Sequence in Five Children with Prenatal Exposure to Methadone. David W. Smith 33rd annual Workshop on Malformations and Morphogenesis 2012
133. Emily King, Bettsy Leech, Howard Saal, Kevin Stanford, **Robert J. Hopkin**. Need for hospitalization analysis from birth to age 10. 8th Biennial International 22q11.2 Conference Orlando FL. Platform presentation 2012

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134. Carlos E. Prada, **Robert J. Hopkin**, Laurie Bailey, Anne M. Lovell, Nancy D. Leslie, Gregory A. Grabowski. Gaucher disease type 2: outcomes of enzyme replacement therapy and impact on quality of life. ASHG 2012 poster
135. Frits A. Wijburg, Bernard Bénichou, Daniel G. Bichet, Gabriela Dostalova, Lorne Clarke, Alejandro Fainboim, Andreas Fellgiebel, Cassiano Forcelini, Kristina An Haack, **Robert Hopkin**, C. Ronald Scott, Suma Shankar, Anna Tytki-Szymanska, Camilla Tøndel, Uma Ramaswami. A Randomized, Multicenter, Multinational, Phase 3B, Open-Label, Parallel-Group Study of Agalsidase Beta in Treatment-Naïve Male Pediatric Patients with Fabry Disease Without Severe Symptoms: Baseline Demographics and Clinical Data. WORLD 2013 Poster
136. **Robert J. Hopkin**, Michael Mauer, Roberta Lemay, Jose Ortiz, Katherine B. Sims, Stephen Waldek. Early initiation of agalsidase beta treatment is associated with fewer clinical events in women with Fabry disease: data from the Fabry Registry. WORLD 2013 Poster
137. Clay, C. D.; **Hopkin, R.**; Wehmeyer, C.; et al Evaluation of Agalsidase Beta specific serum IgE in patients with Fabry Disease. Annals of Allergy Asthma & Immunology Vol 111 supplement 1 A3-A4. 2013
138. Emily King, Bettsy Leech, Howard Saal, Kevin Stanford, **Robert J. Hopkin**. Children with 22q11.2 Deletion Syndrome (Velocardiofacial Syndrome) Experience Increased Medical Interventions Compared to Peers. ACMG 2013 Poster
139. Bous, SM. **Hopkin, RJ**. Smith, DL. Kline-Fath, B. Non-syndromic holoprosencephaly in two siblings: Molecular diagnosis and management. ACMG 2013 Poster
140. Brazil A, Stanford K, Smolarek T, **Hopkin RJ**. Further Delineation of 1p36 Deletion Syndrome in Adolescents and Adults. NSGC meeting 2013 Poster
141. Gladstone A, **Hopkin RJ**, Peay H, Lander J, Wong B, Walker M. Benefits of Genetic Counseling for Parents who have Adopted a Child with Duchenne or Becker Muscular Dystrophy. NSGC meeting 2013 Poster
142. Scott J, Smith N, **Hopkin R**. Challenges to nondirective genetic counseling in the prenatal setting: a case report of multiple anomalies in the fetus NSGC meeting 2013 Poster
143. Brazil A, Stanford K, Smolarek T, **Hopkin RJ**. 1p36 Deletion Syndrome in Adolescents and Adults. David W. Smith 34th annual Workshop on Malformations and Morphogenesis 2013 Platform Presentation
144. Weaver KN, Johnson J, Kline-Fath B, Zhang X, Lim F, Tinkle B, Saal HM, **Hopkin RJ**. The impact of fetal MRI on the prenatal diagnosis of skeletal dysplasias. David W. Smith 34th annual Workshop on Malformations and Morphogenesis Poster 2013 Platform

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145. Bous SM, Weaver KN, Bader PI, Johnson K, Hegde RS, Schorry EK, **Hopkin RJ**. A novel dominant COL11A1 mutation with a sub-lethal fibrochondrogenesis phenotype. David W. Smith 34th annual Workshop on Malformations and Morphogenesis Poster 2013 Poster
146. C Hetteberg, **RJ Hopkin**, A Reponen, M Barve, C Prows. Sustainability and Impact of a Multifaceted Genetics Education Program for Nurses ACMG 2014 Poster
147. Stephanie Santoro, Lisa Martin, **Robert J. Hopkin**. Hematologic Disease in mosaic Down syndrome. ACMG 2014 Poster
148. William R. Wilcox, Ulla Feldt-Rasmussen, Anna Maria Martins, Alberto Ortiz, Frank Weidemann, Roberta M. Lemay, **Robert J. Hopkin**. Female Fabry Disease: Significant Improvement of Fabry disease-related gastrointestinal symptoms in a large cohort of female patients treated with agalsidase beta (Fabrazyme): data from the Fabry Registry. WORLD 2014 Poster
149. Sarah Stueber, Elizabeth Schorry, Lisa Martin, Katie Wusik, and **Robert J. Hopkin**. Impact of Plexiform Neurofibromas on Adult Patients with Neurofibromatosis type 1. NSGC 2014 Poster
150. Dehua Wang, **Robert J Hopkin**, Emily King, Lili Miles, Maria A Calvo-Garcia, Jerzy Stanek. Pena-Shokeir Phenotype/ Fetal Akinesia Deformation Sequence: From Placenta to Secondary Myopathy. IFPA 2014 Poster
151. KN Weaver, KE Noack Watt, KL Sund, RB Hufnagel, T Bender, **RJ Hopkin**, DR Lohmann, D. Wiczorek, PA Trainor, HM Saal. A new mandibulofacial dysostosis syndrome caused by a mutation of POLR1A. David W. Smith 35th annual Workshop on Malformations and Morphogenesis 2014 Platform
152. **Robert J. Hopkin**, Jennifer E. Glass, Teresa A. Smolarek, Howard M. Saal. Trisomy 9 mosaicism should be a diagnostic consideration in CHARGE association. David W. Smith 35th annual Workshop on Malformations and Morphogenesis 2014 Platform
153. Harry Lesmana, **Robert Hopkin**. Maternal UPD (16) with IUGR, transient neonatal hypoglycemia and cholestasis. ASHG 2014 Poster
154. Lesmana H, Dyer L, Smolarek TA, **Hopkin RJ**. Two Cases of Maternal UPD (16) : Phenotypic Evidence of an Imprinting Disorder Affecting Chromosome 16 ACMG 2015 Poster
155. Stephanie Santoro, Lisa J. Martin, Stephen I. Pleatman, **Robert J. Hopkin**. Improving Adherence to the Health Supervision Guidelines for Children with Down Syndrome ACMG 2015 Poster
156. Balow SA, Lesmana H, **Hopkin RJ**, Leslie ND, and Smolarek T. Case Study: Phenotypic evidence for skewed X-inactivation in two siblings with an unbalanced X;22 translocation ACMG 2015 Poster

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157. KN Weaver, KE Noack Watt, RB Hufnagel, J Navajas Acedo, LL Linscott, KL Sund, PL Bender, R König, CM Lourenco, U Hehr, **RJ Hopkin**, DR Lohmann, PA Trainor, D. Wiecezorek, HM Saal. Acrofacial dysostosis, Cincinnati-type: A novel human acrofacial dysostosis caused by POLR1A dysfunction. ACMG 2015 Poster

158. **Robert J. Hopkin**, Gustavo Cabrera, Joel Charrow, Roberta Lemay, Ana Maria Martins, Michael Mauer, Alberto Ortiz, Manesh R. Patel, Katherine Sims, Stephen Waldek, David G. Warnock, William R. Wilcox. Risk Factors for Serious Clinical Events and the Incidence of These Events in Male and Female Patients with Fabry Disease Treated with Agalsidase Beta. WORLD LDN 2015 Platform

159. Robert Wood, Connie Wehmeyer, Laurie Bailey, **Robert J. Hopkin**. Effect of Enzyme Replacement Therapy on Airway Abnormalities in Patients with Hunter Syndrome. WORLD LDN 2015 Poster

160. Bac C, Brazil A, Kummer A, **Hopkin RJ**. Investigation of Speech Delay in Individuals with 1p36 Deletion Syndrome NSGC 2015 poster

161. Rutter MM, Johnson J, **Hopkin RJ**, Saal H, Schwartz B, Breech L, Ernst M, Reddy P, Kennedy K. A tale of two sisters (Frasier syndrome) DSD TRN meeting 2015

162. Lesmana H, Dyer L, Zhou P, Li X, Denton J, Chonat S, Zhang K, **Hopkin RJ**, and Kalfa TA. Alu-Element Insertion in PKLR Gene As a Novel Cause of Severe Hereditary Nonspherocytic Hemolytic Anemia ASH 2015 poster recognized as outstanding research for a trainee.

163. Sophia B. Hufnagel MD1, Martin LJ, **Hopkin RJ**, Cassedy A, Antommaria AH. Adolescents' Opinions on Disclosure of Non-actionable Incidental Findings in Whole Exome Sequencing ASHG Platform presentation 2015

164. Harry Lesmana, Lisa Dyer, Ping Zhou, Xia Li, James Denton, Satheesh Chonat, **Robert J. Hopkin**, Theodosia Kalfa. Novel Alu-Element Insertion in PKLR Gene As A Cause of Severe Hereditary Nonspherocytic Hemolytic Anemia. ASH (American Society of Hematology) meeting 2015

165. David G. Warnock, Daniel G. Bichet, Ademola Abiose, Gustavo Cabrera, Joel Charrow, Dominique P. Germain, **Robert J. Hopkin**, Ana Jovanovic, Aleš Linhart, Sonia S. Maruti, Michael Mauer, Manesh R. Patel, Juan Politei, Stephen Waldek, Christoph Wanner, Han-Wook Yoo, Alberto Ortiz. Lag time to benefit for adult Fabry disease patients on agalsidase beta enrolled in the Fabry Registry GARROD annual meeting 2015

166. Lauren E. Longshore, Cassandra Bac, Stephanie N. Stewart. J. L. Jefferies, **R. Hopkin**, Michael D. Taylor. Left ventricular non-compaction in patients with 1p36 syndrome. American Society of Echocardiography meeting 2015 poster

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167. K. Nicole Weaver, Xue Zhang, Tricia Bender, Zarmina Ehsan, Barbara Chini, **Rob J. Hopkin**, Howard M. Saal. Outcomes of Robin sequence at Cincinnati Children's: a 12-year retrospective analysis. ACPA 2015
168. H.M. Saal, **R.J. Hopkin**, P.L. Bender, K.N. Weaver. Robin Sequence without Cleft Palate: Genetic Diagnoses and Management Implications. ACPA 2015
169. **Robert J. Hopkin**, Amy Ross, Patricia Burns, Michelle Baric, Emily Partack, Foong-Yen Lim. Congenital Diaphragmatic Hernia is genetically complex and associated with many chromosomal abnormalities and syndromes. David W. Smith 36th annual Workshop on Malformations and Morphogenesis 2015 poster
170. R.B. Hufnagel, M.B. Yang, M.E. Gray, L.A. Krueger, T.J. Jaworek, P.L. Bender, P.-W. Chiang, X. Li, T.A. Smolarek, H.M. Saal, **R.J. Hopkin**, Z.M. Ahmed. Molecular and cytogenetic evaluations of atypical anterior segment dysgenesis syndromes with cardiac involvement. David W. Smith 36th annual Workshop on Malformations and Morphogenesis 2015 poster
171. Blake, R. B., Thomas, C. W., Merhar, S., Kline-Fath, B. M., **Hopkin, R. J.**, Bierbrauer, K. S., & Oldham, M. S. (2015). Agenesis of the Corpus Callosum Diagnosed by Fetal MRI: Medical and Developmental Outcomes. In ANNALS OF NEUROLOGY Vol. 78 (pp. S169-S170).
172. Qiao X, Berry L, Bailey L, **Hopkin RJ**, Incidence of lower extremity edema and the effect of diuretics in a population of patients with Fabry disease at a single center WORLD 2016 poster
173. **Hopkin RJ**, Feldt-Rasmussen U, Martins AM, Ortiz A, Weidemann F, Lemay R, Wilcox WR. Improvement of Fabry disease-related gastrointestinal symptoms in a significant proportion of female patients treated with agalsidase beta. WORLD 2016 poster
174. Theobald K, Bale SJ, **Hopkin RJ**, Klein RT, Juusola J, Knapke S, Lim FY, Clinical Whole Exome Sequencing Reveals a De Novo PTPN11 Pathogenic Variant in Association with an Unusual Presentation of Noonan Syndrome ACMG 2016 poster
175. Russell B, Diana Rigueur D, Sund K, Basil J, Hufnagel R, Weaver KN, Prows C, **Hopkin R**, Saal H, Lyons K, Dauber A. A Novel Skeletal Dysplasia Caused by Homozygous Mutations in BMP1A ACMG 2016 platform presentation (awarded David Rimoin Inspiring excellence award for Bianca Russell)
176. Balow SA, Smith N, Russell BE, **Hopkin RJ**, and Smolarek TA. Complex Genomic Rearrangements of the Y chromosome in a Premature Infant ACMG 2016 poster
177. Lesmana H, Hufnagel R, Yang MB, Neilson DE, **Hopkin RJ**. 22q11.2 Microduplication Syndrome Presenting with Anterior Segment Dysgenesis : A Case Report and Review of

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Literature. American College of Medical Genetics (ACMG) Meeting, 2016, Tampa, Florida poster

178. Sheikh R, Brazil, A Pilipenko V, **Hopkin RJ**, Family Impact of 1p36 Deletion Syndrome NSGC 2016 poster

179. Russell B, Balow S, Smolarek T, Wood R, **Hopkin RJ**. Deafness infertility syndrome due to STRC-CATSPER2 deletions with concern for respiratory ciliary dysfunction. David W. Smith 37th annual Workshop on Malformations and Morphogenesis 2016 Platform

180. Monteil DC, Wang L, **Hopkin RJ**. Stormorken syndrome: a clearly recognizable and potentially treatable disorder. David W. Smith 37th annual Workshop on Malformations and Morphogenesis 2016 Poster (the Pater Duncan award winner – best poster by a trainee)

181. Weaver KN, **Hopkin RJ**, Bender PL, Saal HM. Robin Sequence without Cleft Palate: Genetic Diagnoses and Management Implications. David W. Smith 37th annual Workshop on Malformations and Morphogenesis 2016 Platform

182. Lombardo R, Kramer E, Sawnani H, **Hopkin RJ**. Atypical Phenotype of a Family with a Novel Non-Polyalanine Tract Mutation in PHOX2B. David W. Smith 37th annual Workshop on Malformations and Morphogenesis 2016 Platform

183. Labilloy A, Stottmann R, Gordon C, Kline-Fath B, Saal H, **Hopkin RJ**. Nager syndrome presenting with osteoporosis in a 10 year-old male with a novel mutation of SF3B4: a case report. ASHG 2016

184. Vena N, Hosseini SA, Rajakaruna C, Burrow TA, Rochford L, **Hopkin RJ**, RIPPLY2: Believe it or not! ASHG 2016 poster

185. Lombardo R, Monteil D, Lesmana H, Goldschmidt M, Abu-El-Hajja M, **Hopkin RJ**. Impact of Genetic Testing on the Diagnosis and Management of Congenital Diarrheal Disorders ASHG 2016 poster (Awarded Reviewers choice Ribbon and noted on the Poster walk)

186. **Hopkin RJ**, Brand E, Feldt-Rasmussen U, Germain DP, Guffon N, Jovanovic A, Kantola I, Karaa A, Lemay R, Martins AM, Wilcox WR, Yoo HW. Burden of Fabry disease in young patients (≤ 30 years of age) who were initiated on enzyme replacement therapy with agalsidase beta: a Fabry Registry analysis. WORLD 2017 poster

187. Ramaswami U, Wijburg FA, Bichet DG, Clarke LA, Dostalova G, Fainboim A, Fellgiebel A, Forcelini C, An Haack K, **Hopkin RJ**, Mauer M, Najafian B, Scott CR, Shankar SP, Thurberg BL, Tøndel C, Tylki-Szymanska A, Bénichou B. A randomized, phase 3B, open-label, parallel-group study of agalsidase beta in treatment-naïve male pediatric patients with Fabry disease without severe symptoms (FIELD study): GL-3 clearance from kidney cells. WORLD 2017 talk

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188. Warnock DG, Oliveira JP, Bichet DG, Yoo HW, Gruskin DJ, **Hopkin RJ**, Lemay R, Politei J, Wanner C, Wilcox WR, Germain DP. Classification of male Fabry patients: Validation of group consensus by survivor analysis for major clinical . WORLD poster
189. Ramaswami U, Wijburg FA, Bichet DG, Clarke LA, Dostalova G, Fainboim A, Fellgiebel A, Forcelini C, Haack KA, **Hopkin RJ**, Mauer M, Najafian B, Scott CR, Shankar SP, Thurberg BL, Tøndel C, Tylki-Szymanska A, Bénichou B. A randomized, phase 3B, open-label, parallel-group study of agalsidase beta in treatment-naïve male pediatric patients with Fabry disease without severe symptoms (FIELD study): GL-3 clearance from kidney cells. WORLD 2017 poster (Talk also presented)
190. Ramaswami U, Wijburg FA, Bichet DG, Clarke LA, Dostalova G, Fainboim A, Andreas Fellgiebel A, Forcelini C, Haack KA, **Hopkin RJ**, Mauer M, Najafian B, Scott R, Shankar SP, Thurberg BL, Tøndel C, Tylki-Szymanska A, Bénichou B. A randomized, phase 3B, open-label, parallel-group study of agalsidase beta in treatment-naïve male pediatric patients with Fabry disease without severe symptoms (FIELD study): GL-3 clearance from superficial skin capillary endothelium. WORLD 2017 poster
191. Wilson H, **Hopkin RJ**, Madueme P, Czosek RJ, Bailey L, Taylor M, Jefferies JL. Characterization of the early cardiac phenotype in Fabry disease WORLD 2017 poster
192. Clemens P, Laforet P, Kacena K, Sanson BJ, **Hopkin RJ**, van der Ploeg A. Title: Long-Term Efficacy of Alglucosidase Alfa in Late-Onset Pompe Disease AAN 2017 poster
193. van der Ploeg A, Clemens PR, **Hopkin RJ**, Kacena K, Sanson BJ, Laforet P. Long-Term Efficacy of Alglucosidase Alfa in Late-Onset Pompe Disease. WORLD 2017 poster
194. Lesmana H, Nizon M, Mehta P, Isidor B, Agrawal P, Vawter M, Schapiro M, Burrow T, Hallinan B, **Hopkin RJ**. CNTNAP1-related Congenital Hypomyelinating Neuropathy. American College of Medical Genetics (ACMG) Meeting, 2017, Phoenix, Arizona (poster)
195. Russell BE, Balow SA, Dyer LM, Smolarek TA, and **Hopkin RJ**. Non-Invasive Prenatal Screening Results Provide a Valuable Clue to Diagnosis of Chromosome 16 Uniparental Heterodisomy. American College of Medical Genetics (ACMG) Meeting, 2017, Phoenix, Arizona (poster)
196. Yadav A, **Hopkin RJ**. ERF-related Craniosynostosis syndrome and short stature: a new association? American College of Medical Genetics (ACMG) Meeting, 2017, Phoenix, Arizona (poster)
197. Long P, Monteil D, Sullivan B, Hoppman N, **Hopkin R**, T. Smolarek T. A Novel Balanced Rearrangement involving chromosomes 9 and 15 in a Patient with Atypical Angelman Syndrome. American College of Medical Genetics (ACMG) Meeting, 2017, Phoenix, Arizona (poster).

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198. Rutter MM, Hornung L, Ernst MM, Breech L, Reddy P, Kennedy K, Schafer-Kalkhoff T, Hoefgen H, Vanderbrink B, Sheldon C, Howell J, **Hopkin R**, Saal H, Johnson J, Antommaria AH, Sandberg DE, Vilain E, Delot E. Prevalence and Characteristics of Patients with Ovotesticular Disorder of Sex Development in the Disorders / Differences of Sex Development Translational Research Network Registry I-DSD 2017 Copenhagen (June 29-July 1)
199. Garman J, Leech B, **Hopkin R**, Saal H, Pilipenko V, Martin L. Parental Expectations of Future Functional Outcomes in Children Diagnosed with 22q11.2 Deletion Syndrome. NSGC 2017 (Poster)
200. **Hopkin RJ**, Hufnagel R. Mutation c.925C>T (p.Arg309Trp) in MECP2 causes a syndromic form of intellectual disability that is distinct from Rett syndrome. David W. Smith 38th annual Workshop on Malformations and Morphogenesis 2017 Poster
201. Lombardo RC, Cnota J, **Hopkin RJ**. Congenital Heart Disease and Aortic Arch Variants Associated with Mutation in PHOX2B David W. Smith 38th annual Workshop on Malformations and Morphogenesis 2017 Poster
202. Monteil DC, **Hopkin RJ**. Occasionally, William Ockham got it wrong. David W. Smith 38th annual Workshop on Malformations and Morphogenesis 2017 Poster
203. Ramaswami U, Bénichou B, Bichet DG, Clarke LA, Dostalova G, Fainboim A, Fellfiebel A, Forcelini C, Haacki KA, **Hopkin RJ**, Mauerk M, Najafian B, Scott CR, Shankar SP, Thurberg BL, Tøndel C, Tylki-Szymanska A, Wijburg FA. Randomized Controlled Trial of Two Low-Dose Agalsidase Beta Regimens in Male Pediatric Patients with Fabry Disease: GL-3 Clearance from Kidney Cells. ICIEM 2017 Rio de Janeiro
204. Warnock DG, Oliveira JP, Bichet DG, Yoo HW, Gruskin DJ, **Hopkin RJ**, Lemay R, Politei J, Wanner C, Wilcox WR, Germain DP. Classification of male Fabry patients: Validation of group consensus by survivor analysis for major clinical events. ERA-EDTA 2017
205. Aditi Yadav, **RJ Hopkin**, Elizabeth K Schorry. SOPH syndrome; multisystem disorder with facial dysmorphism, skeletal dysplasia, episodic liver failure, immune dysfunction and intellectual disability ASHG 2017
206. Divya Khattar, **RJ Hopkin**. Report of phenotypic variability of periventricular nodular heterotopia in a four-generation Caucasian family with a novel FLNA mutation ASHG 2017
207. Deema Aljeaid, RC Lombardo, DP Witte, **RJ Hopkin**. Novel Pathogenic Variant in OFD1 Results in Male Lethal Oral Facial Digital Syndrome Type 1 with Pituitary Aplasia. ASHG 2017
208. Simpson, B, H Saal, **RJ Hopkin**. Microdeletion of Xp22 encompassing SHOX and ARSE, showing incomplete penetrance and variable expressivity. ASHG 2017

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209. Russell B, Labilloy A, Whaley K, Lombardo R, Bove K, Muglia L, Prada C, **Hopkin RJ**, Leslie N, Assouline Z, Barcia G, Bouchereau J, Chomton M, Debray D, Dorboz I, Durand P, Guettier-Bouttier C, Habes D, Jardel C, Labarthe F, Lévy J, Lombès A, Mehler Jacob C, Melki J, Menvielle L, Munnich A, Pichard S, Rio M, Rötig A, Sissaoui S, Slama A, Miethke A, Schiff M. Expanding and Underscoring the Hepato-Encephalopathic Phenotype of QIL1/MIC13: A Recently Described Mitochondrial Contact Site and Cristae organizing system (MICOS) Complex Gene. American College of Medical Genetics (ACMG) Meeting, 2018 Charlotte, NC (poster)
210. Sullivan B, Aljeaid D, Wusik K, Neilson D, **Hopkin R**. Wiedemann-Steiner Syndrome: Expansion of the Phenotype Featuring Two Cases with Previously Unreported Features and Review of the Literature. American College of Medical Genetics (ACMG) Meeting, 2018 Charlotte, NC (poster)
211. Monteil DC, Weaver KN, Yadav A, **Hopkin RJ**. Blurring the Lines: The KAT6B Continuum - Say Barber Biesecker Young Simpson Syndrome and Genitopatellar Syndrome. American College of Medical Genetics (ACMG) Meeting, 2018 Charlotte, NC (poster)
212. Wilcox WR, Fomin VV, Germain DP, Goker-Alpan O, Golán L, Hiwot T, **Hopkin RJ**, Hughes DA, Jovanovic A, Lukina E, Mange KC, Sensinger C, Tyłki-Szymańska A, Wallace E, Deegan P. A phase 2a study to evaluate the safety, pharmacokinetics, pharmacodynamics, and exploratory efficacy of venglustat in adult male Fabry patients. American College of Medical Genetics (ACMG) Meeting, 2018 Charlotte, NC (poster)
213. Lombardo RC, **Hopkin RJ**. NextGen and Whole Exome Sequencing in Atypical Cerebral Palsy: Demystifying the Diagnosis. American College of Medical Genetics (ACMG) Meeting, 2018 Charlotte, NC (poster)
214. Champion MW, **Hopkin RJ**, Goldgar C, Prows C, Dasgupta S. Educating the Next Generation of Genetic Service Providers (symposium at ACMG 2018) Moderator and presenter of Genetic Residency Training. American College of Medical Genetics (ACMG) Meeting, 2018 Charlotte, NC (Moderator and platform presentation)
215. Passarge E, Ziegler AN, **Hopkin RJ**, Saal HM. A fifty-year follow-up of familial Hirschsprung disease. German Society of Human Genetics meeting Münster 2018
216. Sullivan B, Embresh M, Widmeyer KL, Geller J, Miethke A, **Hopkin RJ**. ERCC1-related nucleotide excision repair defect is a novel disease characterized by microcephaly, developmental delay, and predisposition to cancer: enhancing the phenotype and providing a management plan. David W. Smith 39th annual Workshop on Malformations and Morphogenesis 2018 (Poster)
217. Simpson B, Khattar D, Choo D, Wiley S, Marcheschi L, Scott D, Lalani S, **Hopkin RJ**. CHARGE Syndrome in the Era of Molecular Diagnosis: Need for Higher Clinical Suspicion - Findings in the CCHMC CHARGE Center Cohort. David W. Smith 39th annual Workshop on Malformations and Morphogenesis 2018 (Platform presentation)

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218. Lombardo RC, Monteil D, Marsh RA, Farrell PR, Kocoshis S, Valencia CA, Leino D, **Hopkin RJ**, Cole CR. Impact of Molecular Diagnosis on Management, Treatment, and Long Term Outcomes in Congenital Diarrheal Disorders. David W. Smith 39th annual Workshop on Malformations and Morphogenesis 2018 (Platform presentation)
219. **Hopkin RJ**, Lombardo RC, Russell B, Aljeaid D, Yadav A, Sullivan BR, Simpson B, Khattar D, Masunga A, Bender PL, Monteil DC. It Actually Matters: utility of a diagnosis for very rare conditions David W. Smith 39th annual Workshop on Malformations and Morphogenesis 2018 (Poster)
220. Jefferies JL, **Hopkin RJ**. Prevalence of Lymphedema in Anderson-Fabry Disease: A Report from the Fabry Registry. American Society of Human Genetics Meeting 2018 (poster)
221. Aljeaid D, **Hopkin RJ**. A Familial Novel Whole CDKN1C Gene Deletion in Siblings with Beckwith-Wiedemann Syndrome and Dandy-Walker Malformation. ASHG 2018 (poster)
222. Khattar D, Smith N, **Hopkin RJ**. Whole Exome Sequencing identifies novel mutation in CHAT gene for a lethal perinatal presentation of hydrops and arthrogryposis multiplex congenital. ASHG 2018 (poster)
223. Schulze KV, Szafranski P, Lesmana H, **Hopkin RJ**, Hamvas A, Wambach JA, Fonseca CMBC, Liu Q, Karolak J, Lupski JR, Hanchard NA, Stankiewicz P. Comparisons of chromosome-wide DNA methylation patterns between maternal and paternal UPD (16) reveal evidence for additional imprinted regions. ASHG 2018 (poster)
224. **Hopkin RJ**, Germain DP, Bichet DG, Gruskind DJ, Lemay R, Oliveira JP, Politei, Wanner C, Wilcox WR, Yooi HW, Warnock DG. A survivor analysis for major clinical events in heterozygous female patients with Fabry disease using group consensus phenotype classifications from hemizygous male patients. WORLD 2018 (poster)
225. **Hopkin RJ**. Utility of Genomic Testing. AAPNGBH November 8 2018 (300 representatives of large companies who are self-insured) Platform presentation and questions
226. Eapen A, Simpson BN, Redmond M, **Hopkin R**, Risma K. A case of Hyper-IgM immunodeficiency presenting initially as a novel syndromic disorder. AAAAI 2019 poster
227. Sunder-Plassmann G, Bichet DG, Davidonis M, Germain DP, Giugliani R, **Hopkin RJ**, Jovanovic A, Linhart A, Nicholls K, Nordbeck P, Feldt-Rasmussen U, Rutecki J, Giuliano J, Skuban N, Politei J. Design of a Prospective, Multicenter, Multinational, Observational Safety and Outcomes Registry in Patients With Fabry Disease Who Are Untreated or Treated with Migalastat or Enzyme Replacement Therapy WORLD 2019 (poster)
228. **Robert J. Hopkin**, Gustavo H. Cabrera, John L. Jefferies, Eva Brand, Ulla Feldt-Rasmussen, Dominique P. Germain, Nathalie Guffon, Ana Jovanovic, Ilkka Kantola, Amel Karaa, Ana M. Martins, William R. Wilcox, Meng Yang, Han-Wook Yoo, Michael Mauer.

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Renal and cardiac outcomes of young male patients with Fabry disease initiated on agalsidase beta treatment before age 30: A Fabry Registry analysis Congresso Paulista de Nefrologia (CPN), São Paulo, Brazil, September 25–28, 2019 (platform presentation)

229. Simpson B, Labilloy A, **Hopkin R**, Prada C. Late-Onset Cognitive Regression in Long-Standing Intellectual Disability European MPS Meeting 2019 (poster)

230. Deegan P, Germain D P, Goker-Alpan O, Geberhiwot T, **Hopkin R J**, Lukina E, Tylki-Szymanska A, Sensinger C, Gaemers S, DasMahapatra P, Modur V, Zaher A, Wilcox W R. Three year open label phase 2a investigation of venglustat safety and exploratory efficacy in classic Fabry patients SSIEM 2019 (platform presentation)

231. **Robert J. Hopkin**, Gustavo H. Cabrera, John L. Jefferies, Eva Brand, Ulla Feldt-Rasmussen, Dominique P. Germain, Nathalie Guffon, Ana Jovanovic, Ilkka Kantola, Amel Karaa, Ana M. Martins, William R. Wilcox, Meng Yang, Han-Wook Yoo, Michael Mauer. Significant abdominal and acute pain improvements in young patients with Fabry disease initiated on agalsidase beta treatment before age 30: a Fabry Registry analysis WORLD 2019 (poster)

232. **Robert J. Hopkin**, Gustavo H. Cabrera, John L. Jefferies, Eva Brand, Ulla Feldt-Rasmussen, Dominique P. Germain, Nathalie Guffon, Ana Jovanovic, Ilkka Kantola, Amel Karaa, Ana M. Martins, William R. Wilcox, Meng Yang, Han-Wook Yoo, Michael Mauer. Renal and cardiac outcomes of young male patients with Fabry disease initiated on agalsidase beta treatment before age 30: a Fabry Registry analysis WORLD 2019 (poster)

233. Jacquelynn Berton, **Robert Hopkin**, Bettsy Leech, Xue Zhang, Brittany Simpson, Sarah Greenwell, Howard Saal. Examining the Relationship Between Parenting Stress and Anxiety in Children with 22q11.2 Deletion Syndrome NSGC annual meeting 2019 (poster)

234. Lauren A. Head and **Robert J. Hopkin**. Case Series of Family with Rare c.925C>T, p.R309W MECP2 Mutation. NSRF 2019

235. Sunder-Plassmann G, Bichet DG, Davidonis M, Germain DP, Giugliani R, **Hopkin RJ**, Jovanovic A, Linhart A, Nicholls K, Nordbeck P, Feldt-Rasmussen U, Rutecki J, Giuliano J, Skuban N, Politei J. Design of a Prospective, Multicenter, Multinational, Observational Safety and Outcomes Registry in Treated and Untreated Patients With Fabry Disease ACMG 2019 (poster)

236. Lauren Ansley Head, Deema Aljeaid, Patricia Lynn Bender, Ethan Tanner-Edwards, Matthew Frazier, Divya Khattar, Rachel C. Lombardo, Abigail Masunga, Danielle C. Monteil, Bianca Russell, Brittany Simpson, Bonnie R. Sullivan, Kathryn Nicole Weaver, Aditi Yadav, **Robert J. Hopkin**. The Utility of Genetic Testing in the Treatment of Rare Diseases ACMG 2019 (poster)

237. Howard M. Saal, Patricia Bender, Bonnie Sullivan, **Robert J. Hopkin**, K. Nicole Weaver. Pierre Robin sequence: High prevalence of chromosomal anomalies ACMG 2019 (poster)

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238. Bonnie R. Sullivan, Beth M. Kline-Fath, Xue Zhang, **Robert J. Hopkin**, K. Nicole Weaver. MRI as a Tool for Prognosis in Fetal Arthrogryposis ACMG 2019 (poster)
239. Yuri A. Zarate, K. Nicole Weaver, **Robert J. Hopkin**, Anatalia Labilloy, Jürgen Spranger, Dan Doherty, Rolf W. Stottmann. GENETIC AND PHENOTYPIC HETEROGENEITY IN KIAA0753- RELATED CILIOPATHIES David W. Smith Workshop 2019 (platform)
240. **Robert J. Hopkin**, Marshall Lukacs, John Gilley, Yi Zhu, Giuseppe Orsomando, Carlo Angeletti, Jianqi Liu, Joun Park, Michael Coleman, Grace Zhai, David Witte, Rolf W. Stottmann. BIALLELIC LOSS OF FUNCTION MUTATIONS IN NMNAT2 CAUSE PRENATAL CONTRACTURES, HYDROPS, BRAIN AND CRANIOFACIAL ABNORMALITIES David W. Smith Workshop 2019 (poster)
241. Rachel C Lombardo, Steve W Wu, **Robert J Hopkin**. SOMETIMES HOOFBEATS ARE ZORSES David W. Smith Workshop 2019 (platform)
242. K Abell, X Zhang, T Bender, **R Hopkin**, H Saal, K Weaver. OUTCOMES FOR PRENATAL DIAGNOSIS OF PIERRE ROBIN SEQUENCE David W. Smith Workshop 2019 (platform)
243. B Simpson, **R Hopkin**, B Kline-Fath, N Weaver. PRENATAL INTRACRANIAL MALFORMATIONS IN JOUBERT SYNDROME David W. Smith Workshop 2019 (platform)
244. S.Bachir, S.Poskanzer, K.Manickam, K. Abell, B .Simpson, C.Goueli, X. Du , N. Weaver, **R. Hopkin**, C. Prada. Phenotypic Expansion and Neuroimaging findings in CSNK2A1: Okur-Chung Neurodevelopmental Syndrome. A Case Series ASHG 2019 (poster).
245. Laney DA, Johnson J, Holida MD, Christensen K, Tapia D, Shore J, Azevedo S, **Hopkin RJ**. Fabry Patient Pathfinder: Pilot Program Fabry appointment companion: a novel tool to improve patient and HCPs communication and satisfaction with disease management. WORLD 2020 (Poster)
246. Bichet DG, Nicholls K, Giugliani R, Hughes DA, Sunder-Plassmann G, Krusinska E, Skuban N, **Hopkin RJ**. Migalastat has a low incidence rate of composite clinical outcomes at long-term follow-up in patients with Fabry disease who previously received enzyme replacement therapy. WORLD 2020 (platform)
247. Sunder-Plassmann G, Bichet DG, Davidonis M, Germain DP, Giugliani R, **Hopkin RJ**, Jovanovic A, Linhart A, Nicholls K, Nordbeck P, Feldt-Rasmussen U, Rutecki J, Giuliano J, Skuban N, Krusinska E, Politei J. Baseline Patient Characteristics of FollowME, a New, Patient-Centric, Prospective, Observational Fabry Registry That Evaluates Migalastat, ERT, and a Natural History Cohort. WORLD 2020 (poster)

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248. **Hopkin RJ**, Yang M, Ponce E, Feldt-Rasmussen U, Germain DP, Jovanovic A, Martins AM, Nicholls K, Ortiz A, Varas C, Weidemann F, Wilcox WR. Improvement of Fabry disease-related gastrointestinal symptoms in significant proportions of classic male patients treated with Agalsidase beta: a Fabry Registry analysis. WORLD 2020 (poster)
249. **Hopkin RJ**, Jefferies JL, Oudit G Cardiovascular Complications in Fabry Disease WORLD 2020 (invited speaker breakout symposium)
250. **Hopkin RJ** Approaches to Treatment for Genetic disease Tiawan association of Genetics annual meeting 2020 (invited speaker)
251. Mauer M, Goker-Alpan O, Germain D, Wilcox W, **Hopkin RJ**, Lukina E, Geberhiwot T, Deegan PK, Tylki-Szymanska A, Sensinger C, Zaher A, Hailman E, Modur V, Najafian B. Classic Disease Glucosylceramide Synthase Inhibition with Venglustat in Fabry Patients Leads to Progressive Reduction of Endothelial Cell Globotriaosylceramide Inclusion Volume. SSIEM 2020 poster
252. Najafian B, Goker-Alpan O, Germain D, Wilcox W, **Hopkin RJ**, Lukina E, Geberhiwot T, Deegan P, Tylki-Szymanska A, Sensinger C, Zaher A, Hailman E, Modur V, Mauer M. Glucosylceramide synthase inhibition with venglustat in classic Fabry disease patients leads to progressive reduction of endothelial cell globotriaosylceramide inclusion volume. ASN 2020 (poster)
253. Di Donato N, Bahi-Buisson, N, Gertler T, Guerrini R, **Hopkin R**, Webster R, Leventer R, Zaki MS, Abdel-Hamid MS, Dinkel P, Pierani H, Pierani A, Dobyns WB. Reelinopathies – a clinical continuum of neurodevelopmental and neuropsychiatric disorders due to mutations in RELN. ESHG 2020
254. Eureka Phillip, Divya Khattar, Timothy Knilans, **Robert Hopkin**. Fatal Cardiac Arrhythmia in a patient with Microphthalmia with Linear Skin Defects Syndrome. EDWARD L. PRATT LECTURE Cincinnati OH 2020 (poster)
255. Divya Khattar, Leandra Tolusso, **Robert Hopkin**. Retrospective Review of Non-Immune Hydrops Fetalis: Prevalence of Genetic Etiology and Outcomes. NIHF 2020 (poster)_
256. Lauren Ansley Head, Jared Iding, Wen Zhong, Ethan Tanner-Edwards, **Robert J. Hopkin** The Utility of Genetic Testing in the Treatment of Rare Diseases. ACMGG 2020 (poster)
257. Divya Khattar, Carlos E Prada, Barbara E Hallinan, **Robert J Hopkin**. Expanding the Neurodevelopmental Phenotype of Asparagine Synthetase Deficiency. ACMGG 2020 (poster)
258. Sullivan BR, Kline-Fath BM, Zhang X, Saal HM, **Hopkin RJ**, Weaver KN. Using Fetal MRI as a Guide for Prognosis in Prenatally Diagnosed Arthrogryposis. ACMGG 2020 (poster)

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259. K Abell, **RJ Hopkin**, PL Bender, F Jackson, K Smallwood, RW Stottmann, HM Saal, KN Weaver. MANDIBULOFACIAL DYSOSTOSIS WITH MICROCEPHALY: COHORT EXPANSION David W. Smith Workshop 2020 (platform)
260. S Bachir, K Abell, S Pradhan, X Hu, B Leech, S Chandra, A Misfeldt, **RJ Hopkin**. Sudden Death During Recovery Phase in Two Children with Complex Genetic Syndromes and COVID-19. ASHG 2020 (poster)
261. Baker EK, Weaver KN, **Hopkin RJ**. Further Expansion and Confirmation of Phenotype in Rare Loss of YWHAE Gene Distinct From Miller-Dieker Syndrome. ACMG 2021 (Poster)
262. Laney DJ, **Hopkin RJ**, Rastogi A. Exploring the implications of variants of unknown significance in Fabry disease. ACMG 2021 (invited speaker breakout symposium)
263. Ramaswami U, Leonowens C, Goker-Alpan O, Wilcox RW, **Hopkin RJ**, Sanchez-Valle A, Schmith V, Skuban N, Johnson F. Migalastat 150mg Every Other Day Achieves Bioequivalent Exposures in Adult and Adolescent Patients with Fabry Disease. WORLD 2021 (Poster)
264. Tchan M, Bratkovic D, Nicholls K, **Hopkin R**, Sunder-Plassmann G, Hughes D, Krusinska E, Veleva-Rotse E. Long-term multisystemic efficacy with migalastat in ERT-naive and ERT-experienced patients with amenable GLA variants. WORLD 2021 (platform)
265. Bratkovic D, Tchan M, Nicholls K, **Hopkin R**, Sunder-Plassmann G, Hughes D, Krusinska E, Veleva-Rotse E. Long-term multisystemic efficacy with migalastat in ERT-naive and ERT-experienced patients with amenable GLA variants. ICIEM 2021 (platform)
265. **Hopkin R**, Braun Fabian, Iaccarino G, Bekri S. Uncovering multiple mechanisms of Fabry disease – implications for management. WORLD 2021 (breakout symposium chair and speaker)
266. Shillington A, **Hopkin R**, Zappia K, Lamy M, Erickson CA, Pedapati EV, Dominick KC. Exploring genetic risk variants in patients with autism spectrum and other neurodevelopmental disorders with comorbid catatonia: variants of interest in synaptic signaling pathways. INSAR 2021 (Platform and poster)
267. Wong M, Pilipenko V, **Hopkin R**, Berry L, Bailey L. Abstract: The disease status of patients with Fabry disease using Galafold (migalastat) at CCHMC: a retrospective chart review. NSGC 2021 (poster)
268. Conley NL, Rutter MM, Ernst MM, Schaefer-Kalkhoff T, **Hopkin R**, Saal H, Johnson J, Myers M. Factors influencing the decision to share information about differences of sex development among adolescents and young adults. NSGC 2021 (poster)
269. EK Baker, B Pode-Shakked, **RJ Hopkin**, RW Stottmann PhD; KN Weaver. MDPPP2R1A Neurodevelopmental disorder is associated with congenital heart defects. Smith Meeting 2021 (platform)

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270. **Hopkin RJ**, Shillington A, Lamy M, Dominick K, Erickson C. Psychiatric disease and intellectual disability a common high yield indication for genetic evaluation. Smith Meeting 2021 (Platform)
271. Berklite L, Lopez Nunez O, Bondoc A, Kim H, Bachir S, Somers K, Drach A, Talbott C, Fortener A, Nagarajan R, **Hopkin R**, Szabo S. Embryonal Rhabdomyosarcoma (ERMS) of the Diaphragm in Basal Cell Nevus Syndrome (BCNS): A Case Report and Review of the Literature. Society of Pediatric Pathology 2021 (poster)
272. Ganesh J, Goker-Alpan O, **Hopkin RJ**, Bernat J, Deegan P, Cao L, Chen M, Jaggumantri S, Passalacqua C, Souberbielle B, Cockcroft BM. A Phase I/II multicenter gene therapy clinical study for Fabry disease. ICIEM 2021 Australia (poster)
273. Bratkovic D, Tchan M, Nicholls K, **Hopkin R**, Sunder-Plassmann G, Hughes D, Krusinska E, Veleva-Rotse B. Long-term multisystemic efficacy with migalastat in ERT-naïve and ERT-experienced patients with amenable GLA variants. ICIEM 2021 Australia (poster)
274. Ramaswami U, Wilcox W, **Hopkin RJ**, Yang H, Jiang H, Lengoc V. Migalastat HCl 150 mg every other day is well-tolerated and efficacious in adolescent patients with Fabry disease WORLD 2022 (platform)
275. **Hopkin RJ**, Bichet DG, Sunder-Plassmann G, Nicholls K, Olivotto I, Giugliani R, Krusinska E, Veleve-Rotse B, Hughes D. Long-term multisystemic efficacy with migalastat in ERT-naïve and ERT-experienced patients with amenable GLA variants. WORLD 2022 (poster)
276. Hughes D, **Hopkin RJ**, Bichet DG, Sunder-Plassmann G, Nicholls K, Olivotto I, Giugliani R, Krusinska E, Veleva-Rotse B. Long-term multisystemic efficacy with migalastat in ERT-naïve and ERT-experienced patients with amenable GLA variants. WORLD 2022 (poster)
277. Nordbeck P, Jovanovic A, Pisani A, Nowak A, Feldt-Rasmussen U, Brand E, Hughes D, Bichet DG, West M, Nicholls K, **Hopkin RJ**, Giugliani R, Politei J, Rutecki J, Giuliano J, Krusinska E, Sunder-Plassmann G. Baseline demographics and clinical characteristics of patients enrolled in the followMEFabry Pathfinders registry. WORLD 2022 (poster)
278. Saenz Ayala S, Berry L, Hagen L, **Hopkin R**, Pena L. Insights on genotype-phenotype correlations for Pompe disease in the NBS era. WORLD 2022 (poster)
279. Ganesh J, Goker-Alpan O, **Hopkin RJ**, Bernat J, Deegan P, Cao L, Chen M, Jaggumantri S, Passalacqua C, Souberbielle B, Cockcroft BM. Preliminary Results of the STAAR Study, a Phase I/II Study of Isargalgene Civaparovvec (ST-920) Gene Therapy in Adults With Fabry Disease WORLD 2022 (platform)
280. **Hopkin R**, Kupferman J, Deegan P, Minini P, Goyeau H, Maski M, Lyn N, DasMahapatra P, Germain DP. A study to evaluate the effect of venglustat on neuropathic and abdominal pain in symptomatic adult patients with Fabry disease. WORLD 2022 (poster)

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281. Desai AK, Li C, Gupta P, Dempsey K, Bhambhani V, **Hopkin R**, Ficicioglu C, Tanpaiboon P, Craigen WJ, Rosenberg AS, Kishnani PS. Transforming the clinical outcomes in CRIM-negative infantile Pompe disease identified via newborn screening: the benefits of early treatment with enzyme replacement therapy and immune tolerance induction. WORLD 2022 (poster)

282. Gittens OE, Brightman DS, Qu'd D, **Hopkin RJ**, Halley Wasserman HL, and Simpson BN. High Prevalence of Bony Abnormalities in Patients with Rubinstein-Taybi Syndrome: A Case Series ACMGG 2022 (poster)

283. Owens J, **Hopkin RJ**, Simpson BN. Genotype / Phenotype Correlations in Joubert Syndrome. ACMGG 2022 (poster)

284. Laney D, Rastogi A, **Hopkin RJ**. A multidisciplinary conversation on the stories of women with Fabry disease. ACMGG 2022 (invited symposium CME program)

285. Jovanovic A, Nordbeck P, Pisani A, Nowak A, Feldt-Rasmussen U, Brand E, Hughes D, Bichet DG, West ML, Nicholls K, **Hopkin RJ**, Giugliani R, Politei J, Veleza-Rotse B, Rutecki J, Giuliano JD, Krusinska E, Sunder-Plassmann G. Clinical characteristics of female patients enrolled in the FollowME Fabry Pathfinders registry. SSIEM 2022 (poster)

286. Passalacqua C, Ganesh J, Goker-Alpan O, **Hopkin RJ**, Bernat J, Deegan P, Cao L, Chen M, Jaggumantri S, Bowden E, Shiue L, Souberbielle B, Cockroft BM. Preliminary Results of the STAAR Study, a Phase 1/2 Study of Isaralgagene Civaparvovec (ST-920) Gene Therapy in Adults With Fabry Disease. Fabry Update 2022 (poster)

287. Bichet DG, **Hopkin RJ**, Sunder-Plassmann G, Nicholls K, Olivotto I, Giugliani R, Krusinska E, Veleza-Rotse B, Hughes D. Long-term multisystemic efficacy with migalastat in ERT-naïve and ERT-experienced patients with amenable GLA variants. Fabry Update 2022 (platform)

288. Nordbeck P, Jovanovic A, Pisani A, Nowak A, Feldt-Rasmussen U, Brand E, Hughes D, Bichet DG, Azevedo O, West ML, Nicholls K, **Hopkin RJ**, Giugliani R, Politei J, Rutecki J, Giuliano J, Krusinska E, Sunder-Plassmann G. Baseline demographics and clinical characteristics of patients enrolled in the followME Fabry Pathfinders registry. Fabry Update 2022

289. Ganesh J, Deegan P, Goker-Alpan O, **Hopkin RJ**, Bernat JA, Wilcox W, Cao L, Chen M, Shiue LH, Bowden E, Jaggumantri S, Passalacqua C, Souberbielle B, Cockroft BM. Preliminary results of STAAR, a Phase I/II study of isaralgagene civaparvovec (ST-920) gene therapy in adults with Fabry disease and long-term follow-up. SSIEM 2022 (poster)

290. Ganesh J, Deegan P, Goker-Alpan O, **Hopkin RJ**, Bernat JA, Wilcox W, Cao L, Chen M, Shiue LH, Bowden E, Jaggumantri S, Passalacqua C, Souberbielle B, Cockroft BM. Preliminary

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results of STAAR, a Phase I/II study of isaralgagene civaparvovec (ST-920) gene therapy in adults with Fabry disease and long-term follow-up. NORD 2022 (platform)

291. P Deegan, J Ganesh, O Goker-Alpan, **R Hopkin**, J Bernat, W Wilcox, L Cao, M Chen, L Shiue, E Bowden, S Jaggumantri, C Passalacqua, B Souberbielle, BM Cockcroft. Preliminary results of STAAR, a Phase I/II study of isaralgagene civaparvovec (ST-920) gene therapy in adults with Fabry disease and longterm follow-up. ESGCT 2022 (platform)

292 Yu L Rutter MM, Johnson J, Ernst MM Antommaria A, **Hopkin R**, Strine A, Pennesi C. Decision-making Regarding Gonadectomy in Patients with 17 β -Hydroxysteroid Dehydrogenase Type 3 Deficiency 46,XY Difference of Sex Development (DSD). NASPAG 2022 (poster)

293. Pandurangi S, Malik A Valencia A, Karns R, Marsh R, Kasten J, Huggins J, Gutierrez Sanchez LH, Castro-Rojas C, Eloiseily E, Grom A, Owens J, **Hopkin RJ**, Miethke AG. Deleterious variants in TNFAIP3 are associated with Type II and Seronegative Pediatric Autoimmune Hepatitis. AASLD 2022 (poster)

294. **Hopkin RJ**, Belonis A, Lombardo RC, Qu d D, Saal HM, Simpson BN. SRCAP variants in 2 families with phenotypes inconsistent with floating harbor syndrome. Smith Meeting 2022 (platform)

295. Lander JM, Thomas C, **Hopkin RJ**. STAG2 as a Novel Cause of Atelencephaly. Smith Meeting 2022 (poster)

296. Owens JW, **Hopkin RJ**, Simpson BN. Phenotypic Variance in Joubert Syndrome Partially Explained by Ciliary Pathophysiology. Smith Meeting 2022 (platform)

297. Shillington A, **Hopkin RJ**, White L, Harris K, Lamy M. Delivering clinical genetic evaluation and testing for patients with neurodevelopmental disorders in the inpatient psychiatry setting may reduce inpatient hospital stays and improve clinical outcomes. ACMG 2023 (Platform Shillington)

298. Jovanovic A, Nordbeck P, Pisani A, Nowak A, Feldt-Rasmussen U, Brand E, Hughes D, Bichet DG, West ML, Nicholls K, **Hopkin RJ**, Giugliani R, Politei J, Veleva-Rotse, Rutecki J, Giuliano JD, Krusinska E, Sunder-Plassmann G. Clinical characteristics of female patients enrolled in the FollowME Fabry Pathfinders registry. WORLD 2023 (Poster Jovanovic)

299. Berry L, **Hopkin R**, Raymond T. Fabry Disease Coinciding with Pathogenic Variant Autosomal Dominant Hereditary Transthyretin Amyloidosis - Which is the Red Herring? WORLD 2023 (Poster)

300. **Hopkin RJ**, Ganesh J, Deegan P, Goker-Alpan G, Bernat J, Wilcox W, Pahl M, Whitley C, Hughes D, Nicholls K, Cao L, Chen M, Shiue L, Bowden E, Jaggumantri S, Passalacqua C, Souberbielle B, Cockcroft BM. Safety, biomarkers, and cardiac efficacy in STAAR, a Phase I/II study of isaralgagene civaparvovec (ST-920) gene therapy in adults with Fabry disease and long-term follow-up. WORLD 2023 (Platform)

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301. Wallace EL, Goker-Alpan O, Wilcox WR, Holida M, Bernat J, Longo N, Hughes D, Giraldo P, Molnar MJ, Ortiz D, **Hopkin RJ**, Tøndel C, Linhart A, Deegan P, Jovanovic A, Muriello M, Barshop BA, Kimonis V, Vujkovic B, Nowak A, Hiwot TG, Pisani A, Germain DP, Kantola I, Knoll J, Mehta A, Waldek S, Almon E, Alon S, Chertkoff R, Rocco R, Warnock DG. First results of a head-to-head trial of pegunigalsidase alfa vs. agalsidase beta in Fabry disease: 2 year results of the phase 3 randomized, double-blind, BALANCE study WORLD 2023 (platform Wallace)

302. **Hopkin RJ**. Management Of Fabry disease. 6th International LSD Forum. Toykyo Japan 30 MAR-1 APR 2023 (Invited Platform)

303. Warnock DG, Bernat J, Goker-Alpan O, Wilcox WR, Holida M, Longo N, Hughes D, Giraldo, P, Molnar MJ, Ortiz D, **Hopkin RJ**, Tondel C, Linhart A, Deegan P, Jovanovic A, Muriello M, Barshop BA, Kimonis V, Vujkovic B, Nowak Am Hiwot TG, Pisani A, Germain DP, Kantola, I, Knoll J, Mehta A, Waldek S, Almon E, Alon Sm Chertkoff R, Rocco R Wallace E. Head-to Head Trial of Pegunigalsiase Alfa vs. Agalsiase Beta in Fabry disease: Phase 3 Randomized Double-Blind BALANCE Study 2-year Results. ACMG 2023 (poster)

304. Lander JM, Ayyala R, Thomas C, **Hopkin RJ**. STAG2 is a Novel Genetic Cause of Atelencephaly. ACMG 2023 (Poster)

305. Owens JW, **Hopkin RJ**, Alvey L, Viswanath V, Shillington A. Hands-On Research Experience through a Case Report Writing Workshop Increases Trainee Engagement in Clinical Genetics. ASHG 2023 (poster)

306. NordbeckP, Hughes DA, Nowak A, **Hopkin RJ**, Veleva-Rotse B, Krusinska E, Jovanovic A. Multiorgan involvement in females with Fabry disease: results from 2 phase III trials and the followME registry. SSIEM 2023 (Poster)

307. Hughes DA, Nordbeck P, Pisani A, Nowak A, Feldt- Rasmussen U, Brand E, Jovanovic A, . Bichet DG, West ML, Nicholls K, **Hopkin RJ**, Giugliani R, Politei J, Veleva-Rotse BO, Rutecki J, Giuliano JD, Krusinska E, Sunder-Plassmann G. Clinical characteristics of female patients enrolled in the FollowME Fabry Pathfinders registry. BIMDG 2023 (poster)

308. Hughes DA, Nordbeck P, Pisani A, Nowak A, Feldt- Rasmussen U, Brand E, Jovanovic A, . Bichet DG, West ML, Nicholls K, **Hopkin RJ**, Giugliani R, Politei J, Veleva-Rotse BO, Rutecki J, Giuliano JD, Krusinska E, Sunder-Plassmann G. Clinical characteristics of female patients enrolled in the FollowME Fabry Pathfinders registry. NH (National Health Service) 2023 (poster)

309. Garzon J, Aschbacher-Smith L, Patete A, Hankins M, Weisman AG, Serbinski C, Kim K, Sawin M, Qu'd D, Kelly-Mancuso G, Zeid J, Weaver KN, **Hopkin RJ**, Saal HM, Charrow J, Schorry E, Listernick R, Simpson BN, Prada CE. The Long and Short of it- Expanding the Phenotype of NF1 Microdeletion Syndrome. Children's Tumor Foundation 2023

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310. Lombardo R, **Hopkin R**. PURSUING FOR THE PATIENT. Smith meeting 2023 (platform)

311. **Hopkin RJ**. How can you do something so sad and hopeless?
Perspectives gained from trisomy 13 and 18. Smith Meeting 2023 (platform)

312. Zarate YA, Wang B, Zackai E, Weaver KN, Hurst A, Gonzalez A, Graham J, Grand K, Ritter A, **Hopkin R**, Bailey L, Bhoj E, Solocum RB. WHEN FAMILIES MAKE THE GENETIC DIAGNOSIS BEFORE CLINIC: A NARRATIVE MEDICINE PERSPECTIVE. Smith Meeting 2023 (platform)

313. West ML, **Hopkin RJ**. Fabry disease, should all individuals receive therapy? (invited presentation debate format) ACMG 2024 (platform)

314. Rehman AU, Thomas-Wilson A, Mau-Them FT, Tolusso LK, Abyankar A, Guha S, Okur V, Felice V, **Hopkin RJ**, Wilson AL, Han T, Guan Q, Giordano J, Brehin A, Wapner R, Jobanputra V. RNA Sequencing Improves Assessment of Variants of Uncertain Significance From Fetal Genome and Exome Sequencing. ACMG 2024 (poster)

315. Lopez E, Suhas P, Mirabella OK, Sperry ED, Widmeyer K, Hijazi G, Wu Y, Shillington A, Antommaria A, **Hopkin RJ**. Complex Medical Management and Ethical Considerations in Foster Care Twins with Congenital Disorder of Glycosylation Type 1A. ASHG 2024 (poster)

316. Roberts M, Byrne BJ, Dimachkie MM, **Hopkin RJ**, Kishnani PS, Mozaffar T, Schoser B, van der Ploeg AT, Brudvig J, Fox B, Holdbrook F, Jain V, Johnson F, Zhang J, Parenti G. Miglustat: a first-in-class enzyme stabiliser for late-onset Pompe disease. SSIEM 2024 (poster)

317. Khan A, Nordbeck P, Hughes DA, Nowak A, **Hopkin RJ**, Veleva-Rotse B, Krusinska E, Jovanovic A. Multiorgan involvement in females with Fabry disease: Results from two Phase III trials and the followME registry. Garrod 2024 (poster)

318. Hughes DA, Khan A, Nordbeck P, Nowak A, **Hopkin RJ**, Veleva-Rotse B, Krusinska E, Jovanovic A. Multiorgan involvement in females with Fabry disease: results from two Phase III trials and the followME registry. BIMDG 2024 (poster with platform)

Teaching and Mentoring

Teaching

a. Lectures

I have given approximately 50 lectures and talks per year on a wide variety of genetic topics and for many different audiences (complete list available on request)

For 2021 I gave 51 formal presentations. The nature of presentations was much different than usual with more pre-recorded presentations and many on-line.

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b. Medical Students

1. Senior Clinician Rounds twice monthly rounds with medical students (6-14) focus on genetic syndromes. 2 hours. This program selected senior faculty in each specialty to teach physical examination and history taking skills pertinent to their field. I was invited as a new assistant professor in recognition for dedication to medical education 2000-2003
2. Pediatric Ward attending supervision of rotating medical students for 1-4 weeks per year 2000- 2003
3. Preceptor for medical student discussion of problem-based learning cases annually 1 month per year 2000 to 2013
4. Genetics in Primary Care project 2000-2003 Part of a team that developed educational materials on Genetics for Family Medicine, Internal Medicine and Pediatrics. These were designed to be used by the attending physicians in these specialties to teach residents and medical students. We also developed presentations for the same learners but designed for presentation by geneticists or developmental pediatricians. This was a national project. Locally we did 4-5 presentations per year during the funded portion of this program and continued using many of the materials for several years after the funded portion was complete.
5. Lecture on medical genetics to medical students as part of their pediatric rotation every month, 2003-2011
6. Faculty mentor of Genetics Interest Group (initial enrollment approximately 25 students) 2012-present
Note in 2012-2013 this group received formal recognition from the ACMG.
7. Planned and coordinated adding lectures on several genetic topics to the medical school curriculum (in 2012-2014 that included approximately 10 new 1 hour presentations to the medical student class of 150 students I gave 4-5 of these talks other faculty gave the others) These lectures are still provided annually as of 2020.
8. Rotation director for 1 week mini-rotation in Genetics for approximately 45 3rd medical students per year 2017-present (not included in the 2020 calendar year) For this we developed a student genetic experience passport that has kinds of experiences listed to be used as a guide for the students during that week and allows evaluation even when multiple supervisors are involved during a relatively brief rotation by requiring the supervisor for each experience to sign that it was adequately completed.
9. Rotation director for 2-4 week genetics elective for 4th year medical students 5-10 per year 2006-2017 then decreased to 1-5 per year (2006-present)

c. Residents (not training in Genetics)

1. Pediatric Ward Attending Physician 2 week blocks 2-3 times per year 1998 to 2003, and 2007-2011
2. Attend and participate in Pediatric Morning Report weekly Wednesday mornings 1998 to 2008
3. Genetic/dysmorphology rounds: patient selection for, and coordination of weekly 2 hour inpatient teaching rounds for subspecialty fellows, pediatric residents, and medical students 1997-2002

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4. Perinatal rounds (for OB residents) case-based teaching conference approximately 3 cases per year focusing on prenatal diagnosis, genetic counseling, and perinatal management 1997-2003
5. Rotation supervisor and individual instruction of pediatric residents on genetics elective 8-12 residents per year (increased from 6-7), 1997-present (in the 2020 calendar year only a small number of rotators were included because of COVID-19 for 2021 returned to near normal volume)
6. Psychology Colloquium lecture on behavioral phenotypes 1998, 2001-2009
7. Rotation director for MFM fellows rotation in clinical genetics (1-3 per year for 2 months) 2013- present
8. DDBP lecture series: Lectures on dysmorphology and genetics 11/19/1998- present

d. Residents and Fellows in Genetics specialties

1. Genetics Clinic Case conference: 2 hour weekly teaching conference for review of patients seen in genetics clinic 1994-present. I have been the faculty sponsor for CME credit since 2016
2. Genetics in-patient rounds started in 1997 and have been updated and reformatted several times. Currently they serve as a combination teaching rounds and work rounds. They also serve as an opportunity to teach senior residents team leadership skills. We do both an academically oriented virtual version and a clinically oriented face to face version on alternating weeks. 1997-present
3. Didactic lecture series for genetics residents and residents rotating in genetics. This has also been modified and updated several times. It is currently the main resource in our training program for boards review and is attended by genetics residents rotating pediatric /neurology, and other residents as well as laboratory fellows in genetics and genomics. 1999 through present. Current format started 2016
4. Clinical experience for fellows in cytogenetics (now laboratory genetics and genomics) 1-2 per year 2000-present

e. Genetic counseling students

1. In patient teaching rounds for GC students 2003-2004 Weekly bedside teaching on preselected cases with a variety of genetic conditions.
2. Emerging topics in Genetics and Genomics. 2007-present I am currently a speaker and help plan the lecture series. Genetic counseling students are the current primary audience, but genetics residents and laboratory fellows are also invited.
3. Course director for Human Genetics 1 This is a 3-credit graduate level course on Human genetics including cytogenetics, molecular genetics, population genetics and other topics. Approximately 20 students per year 2006-2016

f. Nursing

1. Genetics Institute for nursing faculty 1997-2003, 10-20% commitment
2003-2004 5% commitment
2. Web Based Genetics institute 5-week section on clinical genetics course taught 1-2 times per year 2002-2017.

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The Genetics institute was a grant funded project to develop on-line graduate level training in genetics for nurses initially targeting the faculty in nursing schools who taught genetics courses. The program remained active for 20 years and benefited >200 participants. In a related program we created on-line modules that were self-paced over 15,000 individuals used one or more of those. These resources were taken down in 2018.

Invited lectures, grand rounds, symposia, conferences, workshops, visiting professorships, continuing medical education courses, etc.; include dates and title (this list is limited to 2020-present a complete list can be provided if needed)

1. 2/11/2020 WORLD 2020 Sanofi Genzyme breakout symposium invited panel
Cardiovascular Complications in Fabry Disease
2. 3/18/2020 ACMG breakout symposium invited speaker sponsored by Sanofi Genzyme
Biomarkers for Fabry disease (done as a live stream video presentation)
3. 4/22/2020 Sanofi Genzyme sponsored GME event on Fabry Biomarkers
4. 5/27/202 DSD-TRN video conference on NR5A1 mutations nationwide video conference
from the CCHMC DSD team
5. 9/19/2020 ASN prerecorded invited presentation on Fabry disease for nephrologists
sponsored by Chiesi
6. 10/6/2020 spoke on unmet needs in Fabry disease for 300 business investors for Avrobio
7. 10/16/2020 CCHMC Fetal Care conference presentation on prenatal genetic evaluation to an
audience of >240 OB, MFM, and Neonatologists
8. 10/28/2020 Speaker at the South American launch for Galafold (oral chaperone therapy)
broadcast to multiple countries including Colombia, Brazil, and Argentina
9. 11/21/2020 Invited speaker on emerging treatment for genetic disease at the Taiwan society
of Human Genetics meeting
10. 2/9/2021 Moderator and invited speaker for the WORLD meeting symposium on
Mechanisms of Fabry disease audience >520 viewers
11. 2/10/2021 Invited symposium I was 1 of 4 speakers on Lentiviral Gene Therapy for Fabry
disease with an audience of >400 physicians and scientists
12. 4/14/2021 invited speaker for symposium on variants of unknown significance in Fabry
disease audience >200
13. 4/24/2021 European Academy of Pediatrics Annual Meeting invited speaker on Recognizing
Fabry disease audience >200
14. 4/30/2021 APN annual Conference (regional sponsored by CCHMC) invited speaker on
Dysmorphology audience >200
15. 6/5/2021 Taiwan Academy of Pediatrics invited speaker on Treatment options for Fabry
disease
16. 10/10/2021 AAP NCE Virtual conference invited speaker: Cutting Edge therapies in
Genetics For the neonatology 60 people logged in the day of the presentation but it was
also available on-line
17. 1/28/2022-1/30/2022 AAP Practical Pediatrics invited speaker with 4 different presentations:
 - a. A Practical Approach to suspected genetic syndromes
 - b. Genetic testing from chromosomes to genomes
 - c. Overgrowth syndromes: what we have learned
 - d. The Role of Genetics in Evaluation of AutismThere were 110 pediatricians in attendance for this CME course

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18. 2/8/2022 WORLD Symposium invited speaker for a satellite symposium Fabry disease the impact on women and girls. The audience was approximately 300 people the night of the presentation. The event was video recorded and available on demand for 2022.
19. 2/9/2022 WORLD Symposium invited speaker for a satellite symposium Evaluating Fabry Disease in the Real World. The audience was about 300 people that evening and it was available on demand for 2022.

Participation in patient and family educational activities: include dates and title or brief description (this list is limited to these activities from 2020-present a more complete list can be provided if needed)

1. 3/7/2020 MAGIC foundation Progress in Hypophosphatasia
2. 4/23/2020 Invited presentation COVID-19 and Fabry disease sponsored by Chiesi
3. 5/12/2020 Invited prerecorded video presentation Fabry disease and COVID-19 sponsored by Amicus
4. 6/4/2020 Video presentation on COVID-19 and Fabry disease for approximately 200 patients sponsored by Amicus Therapeutics
5. 7/17/2020 Magic Foundation (National support group) national meeting for 2020 spoke on new discoveries on hypophosphatasia
6. 7/29/2020 national video conference for families on Fabry disease.
7. 10/3/2020 NFDF national meeting (Fabry disease) gave 2 presentations one for adults and one for teens. Total audience >200
8. 11/14/2020 FSIG (Fabry disease support group) National broad cast 200 families signed in for Update on Fabry disease
9. 3/23/2021 NFDF (support group) speaker on Gene Therapy for Fabry disease
10. 4/10/2021 FSIG I gave 2 talks an Update on Fabry disease and Pain Management in Fabry disease
11. 4/24/2021 Fabry International Network (international support group) invited speaker on Sleep Problems in Fabry disease >300 families
12. 7/13/2021 FSIG national broad cast Participation in Clinical Trials (for Fabry disease)
13. 7/17/2021 Magic Foundation (national support group) annual meeting invited speaker Update on Hypophosphatasia
14. 7/17/2021 CHARGE Foundation (national support group) invited speaker on Genetic Testing for CHARGE syndrome
15. 7/24/2021 Invited speaker for the 1p36 support group in the UK London meeting I gave a formal presentation was on an expert panel discussion Q&A and had individual meetings with several families
16. 8/10/2021 NFDF (national support group for Fabry disease) webinar on Fabry disease presentation and management 50 families signed in and it was available online on demand
17. 9/10/2021 NFDF webinar Manifestations of Fabry disease 200 people signed in and it was available on-line
18. 11/30/2021 Ology (produces educational materials for rare diseases) video discussion with 3 women with Fabry disease and a genetic counselor. The audience was patients and families topic was Women with Fabry Disease 60 families for the live broadcast and is available online
19. 2/28/2022 Fabry International Network webinar Update on Fabry disease from the WORLD symposium the audience was patients and families. FIN is an international organization. I

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don't have an estimate of audience size for this year but last year's conference was seen by about 300.

20. 5/7/2022 Fabry International Network (FIN) Invited speaker on-line talk on Gene therapy for an international audience of patient families. 100 live participants and available on demand for 2022

Teaching materials developed (for clinicians, learners, families):

See above for descriptions of online course work developed for nursing, and tools for medical students.

We have also instituted on-line participation options for telehealth, teaching conferences, and even multidisciplinary conferences shared between neurology and Genetics training programs.

In the past I have developed training materials that include pop culture references, dolls, and other resources to engage audiences and decrease anxiety regarding the unfamiliar nature of very rare disease. These have been very effective I have been asked to use the "doll talk" or variations of that theme dozens of times over the years including the current pediatric Noon Conference lecture series.

I am helping develop and implement a Rare Disease University program on Fabry disease that is designed to take clinicians and scientists from introduction to Fabry disease to expert level including mentoring in research project implementation or developing new clinics with state-of-the-art management protocols. This is sponsored by Sanofi Genzyme. We are currently working on a video session focused on the impact of Fabry disease on the whole family (including those who do not have Fabry disease)

Evidence of teaching excellence:

Copies of evaluations available on request

Mentoring

Pediatrics/Genetics Residents

2. Zhao Hui MD, PhD Combined Pediatric /Genetics Residency 7/1/1998 6/30/2003
3. Rope Alan MD Combined Pediatric /Genetics Residency 7/1/1999 6/30/2004
4. Tinkle Brad MD, PhD Combined Pediatric /Genetics Residency 7/1/2000 6/30/2005
5. Kogan Jilene MD, PhD Combined Pediatrics/Genetics Residency 7/1/2001 2/28/2007
6. Burrow T. Andrew MD Combined Pediatrics/Genetics Residency 7/1/2003 6/30/2008
7. Zarate Yuri MD Combined Pediatrics/Genetics Residency 7/1/2004 6/30/2009
8. Rieley Margaret MD Medical Genetics Fellowship 7/1/2007 6/30/2009
9. Prada Carlos MD Combined Pediatrics/Genetics Residency 7/1/2006 6/30/2011
10. George-Abraham Jaya MD Medical Genetics Fellowship 7/1/2009 6/30/2011
11. Broering Tony MD Medical Genetics Fellowship 7/1/2011
12. Sellars Elizabeth MD Combined Pediatrics/Genetics Residency 7/1/2007 6/30/2012
13. Weaver K. Nicole MD Combined Pediatrics/Genetics Residency 7/1/2009 9/14/2014
14. Santoro Stephanie MD Combined Pediatrics/Genetics Residency 7/1/2009 9/22/2014
15. Hufnagel Sophia MD Combined Pediatrics/Genetics Residency 7/1/2010 8/30/2015
16. Hufnagel Robert MD, PhD Combined Pediatrics/Genetics Residency 7/1/2011 6/30/2016

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17.	Monteil Danielle MD Medical Genetics Fellowship	7/1/2014 8/26/2016
18.	Lesmana Harry MD Combined Pediatrics/Genetics Residency	7/1/2012 6/30/2017
19.	Lombardo Rachel MD Combined Pediatrics/Genetics Residency	7/1/2013 7/28/2018
20.	Russell Bianca MD Combined Pediatrics/Genetics Residency	7/1/2013 9/17/2018
21.	Rochford Laura MD Combined Pediatrics/Genetics Residency	7/1/2014
22.	Aljeaid Deema MD Combined Pediatrics/Genetics Residency	7/1/2014 11/17/2018
23.	Yadav Aditi MD Medical Genetics Fellowship	7/1/2016 6/30/2018
24.	Sullivan Bonnie MD Combined Pediatrics/Genetics Residency	7/1/2015 6/30/2019
25.	Labilloy Anatalia MD, PhD Combined Peds/Genetics Residency	7/1/2015 9/22/2019
26.	Simpson Brittany MD Combined Pediatrics/Genetics Residency	7/1/2016 6/30/2020
27.	Khattar Divya MD Combined Pediatrics/Genetics Residency	7/1/2016 6/30/2020
28.	Shillington Amelle DO Combined Pediatrics/Genetics Residency	7/1/2017 6/30/2021
29.	Abell Katherine DO Medical Genetics Fellowship	7/1/2018 6/30/2020
30.	Bachir Suha MD Combined Pediatrics/Genetics Residency	7/1/2018 9/30/2021
31.	Saenz-Ayala Sofia MD Medical Genetics Fellowship	7/1/2019 6/30/2021
32.	Owens Josh MD Combined Pediatrics/Genetics Residency	7/1/2019 6/30/2023
33.	Lander Julie MD, PhD Combined Pediatrics/Genetics Residency	7/1/2019 6/30/2023
34.	Vanagunas Tomas MD, PhD Combined Peds/Genetics Residency	7/1/2020 6/30/2024
35.	Baker Elizabeth MD Medical Genetics Fellowship	9/1/2020 9/14/2022
36.	Ferreira dos Santos, Leonardo, MD Peds/Genetics Residency	7/1/2021
37.	Sperry Ethan, MD. PhD combined Peds/Genetics Residency	7/1/2022
38.	Mirabella Olivia MD Combined Peds/Genetics Residency	7/1/2022
39.	Katz Spencer MD PhD Combined Peds/Genetics Residency	7/1/2023
40.	Plona Katie MD PhD Combined Peds/Genetics Residency	7/1/2023
41.	Hijazi Ghada MD Medical Genetics Fellowship	7/1/2023
42.	Monsberger Ryan MD Medical Genetics Fellowship	7/1/2024
43.	Kreuger Laura MD PhD Combined Peds/Genetics Residency	7/1/2024

All graduates were board certified in Genetics and Pediatrics. All graduates have had publications during residency, average 6 per resident. 18 have given platform presentations at national meetings as residents, some of them had several platform presentations. At least 13 have received 1 or more awards for outstanding research as a trainee at national meetings. As a group there are more than 400 publications from this group since graduating from the CCHMC training program. At least 10 have held significant leadership positions including national committees, and division directors.

International observerships

Aljeaid Deema MD	Rotator Medical Genetics and Genetics	2013 Board certified in Pediatrics
Jawish Rana MD	Rotator Medical Genetics	2015 practicing Psychiatrist
Belhassan Khadija MD	Rotator Medical Genetics	2015 now Board-certified Lab Genetics and Genomics
Sanchez Anna MD	Rotator Medical Genetics	2017 Publications at CCHMC practicing as a geneticist in Colombia
Haithaipat Vaseenon MD (Most)	Rotation Med Genetics	2024 Clinical Genetics in Thailand

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Alvaro Martin, MD Pediatrician in Spain with an interest in Medical genetics 2020-2024 (entered a medical genetics fellowship in 2024).

Genetic Counseling Graduate Students

- Thesis committee member (Stroke) for Jessica Everett genetic counseling M.S. program 1998-1999
- Thesis committee member for Ginger E. Helper genetic counseling M.S. program 1999-2000
- Thesis committee member (Congenital adrenal hyperplasia) for Jen King genetic counseling M.S. program 1999-2000
- Thesis committee member for Marta Wille genetic counseling M.S. program 1999-2000
- Thesis committee member (Breast cancer) for Kerry Howell genetic counseling M.S. program 2000-2001
- Thesis committee member (NF1) for Courtney Drake genetic counseling M.S. program 2001-2002
- Thesis committee chair (22q11.2 deletion) for Michelle Wojtasiak genetic counseling M.S. program 2001-2002
- Thesis committee member for Liz Barry genetic counseling M.S. program 2002-2003
- Thesis committee chair (Fabry disease) for Natalie Jansen genetic counseling M.S. program 2003-2004
- Thesis committee member (carrier testing in adolescence) for Trisha Mulhaupt genetic counseling M.S. program 2003-2004
- Thesis committee chair (research results) for Jill Kelsay genetic counseling M.S. program 2004-2005
- Thesis committee member for Jamie Poskochil genetic counseling M.S. program 2004-2005
- Thesis committee member for Ann Reinhard genetic counseling M.S. program 2004-2005
- Thesis committee chair (Pediatric Fabry disease) for Heather Taylor genetic counseling M.S. program 2005-2006
- Thesis Committee chair (cost for surgery to correct Robin sequence) for Audrey Karlea genetic counseling M.S. program 2006-2007
- Thesis Committee member (international adoption) for Camila Vieira genetic counseling M.S. program 2006-2007
- Thesis Committee member for Andrea Guskowski genetic counseling M.S. 2006-2007
- Thesis Committee chair (22q11.2 deletion) for Kim Cubit genetic counseling M.S. 2008-2009 (project not completed due to student withdrawing from the program this was not related to progress on the thesis research)
- Thesis Committee member (DTC genetic testing) for Ashley Parrott genetic counseling M.S. 2009-2010
- Thesis Committee chair (22q11.2 deletion) for Emily King genetic counseling M.S. 2010-2011
- Thesis Committee member (posterior fossa malformations) for Kyla Patek genetic counseling M.S. 2010-2011

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- Thesis Committee chair (adult Genetics) for Leslie Gress genetic counseling M.S. 2010-2012
- Thesis Committee member (NF1, fractures in adults) for Meron Azage genetic counseling student M.S. 2010-2012
- Thesis Committee member (breast cancer counseling) for Justine Snyder genetic counseling M.S. 2010-2012
- Thesis Committee chair (1p36 deletion) for Ashley Brazil Genetic counseling student M.S. 2011-2013
- Thesis Committee member (adoption and DMD counseling) for Amy Gladstone Genetic counseling student M.S. 2011-2013
- Thesis Committee chair (NF1, plexiform neurofibromas) for Sarah Stueber genetic counseling student M.S. 2012- 2014
- Thesis Committee chair (1p36 deletion, speech problems, cardiomyopathy) for Cassandra Bac genetic counseling student M.S. 2013 –2015
- Thesis Committee chair (1p36 deletion, burden of care) for Rania Sheikh genetic counseling student M.S. 2014-2016
- Thesis committee member (Fabry disease, impact of treatment) for Kait Miller Genetic counseling student M.S. 2014-2016
- Thesis committee chair (22q11.2 deletion parent expectations) for Jamie Garman 2015-2017
- Thesis committee member (22q11.2 deletion speech problems) for Alyxis Giordullo 2015-2017
- Thesis committee member (22q11.2 deletion) for Jacquelyn Berton 2017-2019
- Thesis committee member (22q11.2 deletion anxiety) for Farrah Mahan 2017-2019
- Thesis committee chair (Fabry disease biomarkers when patients switch from Agalsidase beta to migalastat) Melissa Wong 2019-2021
- Thesis committee member (DSD experience from patients) Nathaniel Conley 2019-2021
- Thesis Committee member (Sleep problems in patients with Fabry disease) Jenel Facey 2021-2023
- Thesis Committee member (Gaucher dis.incidental renal anomalies) Zoe Lindsey-Mills 2024-2025

Medical Students

1. Nathan Walker Mentor for Efficient and Cost-Effective Medicine student paper for. BRCA 1/2 testing in women with a positive family history: a cost-efficient analysis. 2000 (award for outstanding project)
2. John Bradshaw Mentor for Efficient and Cost-Effective Medicine student project for. Population Screening for Hemochromatosis. 2003 (award for outstanding project)
3. Fatima Rangwala Mentor for a project on the natural history of plexiform neurofibromas as part of her MD/PhD program. This resulted in a publication Prada CE, Rangwala FA, Martin LJ, Lovell AM, Saal HM, Schorry EK, Hopkin RJ. Pediatric plexiform neurofibromas: impact on morbidity and mortality in neurofibromatosis type 1. J Pediatr. 2012 Mar;160(3):461-7 PMID: 21996156
4. Julie Lander Mentor for her as she established the Genetics Interest Group at the College of Medicine in 2011, she was an MD PhD student and has worked with us for the past 10

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years as she completed her medical school and PhD studies. She also served as a committee member for the thesis project of one of our genetic counseling students 2010-2019 after which she entered a Pediatrics/Genetics residency

5. Lauren Head Mentor for research project on value of making an extremely rare diagnosis 2018- on going has resulted in 3 national meeting presentations (ACMG posters 2019 and 2020 and NSRF 2019 poster). A manuscript is planned for submission.

6. Jared Iding Mentor participation in the project on the value of extremely rare disorders 2020

7. Wen Zhong Mentor participation in the project on the value of extremely rare disorders 2020

8. couple that went to Baylor Met with them several times to review residency applications and career development in Genetics

9. Couple that went to Baylor

10. Courtney Linne Mentor met with her to review residency and career development

Other

I have also mentored undergraduate and high school students on small projects and/or met with them regarding careers in health care or genetics

In 2020 I mentored a high school student (Houston, Texas) on careers in Genetics with 4 formal on-line meetings. I also helped him meet and interview several other geneticists.

Mentorship

Service and Leadership

Service

- Professional organizations:
- American Academy of Pediatrics, Resident Fellow 1993-1996, Candidate Fellow 1997-1998, Fellow 1998-present
- AAP Section on Genetics and Birth defects 1999-2016
- AAP council on Genetics and Genomics 2016-present
- American Society of Human Genetics, 1995-present
- American College of Medical Genetics 2003-present
- Cincinnati Pediatric Society 1998-2019
- National Neurofibromatosis Foundation 1997-present

Committees:

- Task force for review of the genetics content of the medical school curriculum, University of Cincinnati College of Medicine 2001
- Division of Human Genetics Residency Curriculum Committee Chair CHMC 1998-2006
- Pediatric Residency Curriculum Committee CHMC 2001-present
- North American Fabry Registry Board of Medical Advisors 2001-present (Board Chair from 2015-2017)
- Fabry support and information group medical advisory board 2002-present

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- National Fabry Disease Foundation Medical Advisor 2002-present
Asked to be Chair of the Board of Medical Advisors starting January 2022. This is a new position needed because of growth of the organization.
- American Academy of Pediatrics, Section on Genetics and Birth Defects, Subcommittee on Out Comes Research 2001-2005
- American College of Medical Genetics Committee on Therapeutics 2005-2011
- AAP SOGBD Executive Committee 2014-2016
- AAP Council on Genetics and Birth defects Executive Committee 2016-2020 Current projects include revision of the statement on hypothyroidism and development of a statement on Beckwith-Wiedemann syndrome
- AAP Council on Genetics and Genomics Nominations Committee (Responsible for recruitment of nominations for seats on the executive council) 2020-2023
In 2021 we successfully recruited 6 applicants to run for 3 open positions 3 of these were persuaded to join the AAP and or Council on Genetics and Genomics as part pf preparing to run.
- Medical advisor for 1p36 support and information group 2011-present
- International Fabry Registry Advisory Board 2015-2017
- Follow Me Registry Steering Committee (sponsored by Amicus Therapeutics focused on Fabry disease) 2017-present

Manuscript reviews:

- Journal of Pediatrics 2 manuscripts per year 2000-present
- American Journal of Medical Genetics 1-3 per year
- Other journals 2-3 per year
- Recruitment activities:
- Recruitment of Residents for the categorical Genetics training program and the combined Pediatrics/Genetics residency
- Interview applicants for Pediatric residency several per year 1999-2019
- Participation in Division recruitment activities Division of Human Genetics. 1997-present. This includes recommendations for faculty recruitment, interviews and mentorship of new faculty. This has included working with recruitment for the Cyto, Molecular and LGG labs, as well as Clinical genetics providers (both genetic counselors and clinical geneticists).

Community activities:

- Assistant Scout Master, Boy Scouts of America Troop 560. 1998-2000
- Troop committee member for Troop 560 2000-2010
- Annual Camp Physicals for Boy Scouts from Troop 560. (10-15 per year) 1998-2019
- Counselor in the Young Men's organization Church of Jesus Christ of Latter Day Saints Cincinnati First Ward, 1999-2000
- High Counsel Representative, Church of Jesus Christ of Latter Day Saints Cincinnati Ohio Stake, 2000-2001
- Second counselor in the Bishopric, Church of Jesus Christ of Latter Day Saints Cincinnati First Ward, 2001 to 2003
- President of the Young Men's organization Church of Jesus Christ of Latter Day Saints Cincinnati Norwood Ward 2003 to 2007

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- High Priests Group Leader Church of Jesus Christ of Latter Day Saints Cincinnati Ward, Cincinnati OH Stake 2008- 2014
- Counselor in the young men's (ages 12-18) program Church of Jesus Christ of Latter Day Saints Cincinnati Ward 2014-2017
- Second counselor in the bishopric of the Cincinnati Ward, Cincinnati OH Stake in the Church of Jesus Christ of Latter Day Saints November 2017- 2018
- First counselor in the bishopric of the Cincinnati Ward, Cincinnati OH Stake of the Church of Jesus Christ of Latter Day Saints 2018-Jan 2020
- Sunday school president and Sunday school teacher 2020-2022 including institution of on-line Sunday school options
- English Connect instructor (teaching English to French speaking African immigrants meets weekly for 2 hours) 2024-

Leadership

Director of the Medical Genetics residency program at CCHMC 2006-October 2019

Director of the Pediatrics/Medical Genetics combined residency program at CCHMC 2006-October 2019

Director of the Medical Genetics residency program at CCHMC April 2020-present

Director of the Pediatrics/Medical Genetics combined residency program at CCHMC April 2020-present

Distribution of Effort:

Clinical Service	____%
Research and Scholarly Activities	____%
Teaching and Mentoring	____%
Service and Leadership	____%

I have reviewed the curriculum vita for completeness and accuracy and agree with its contents.

Division Director Signature and Date

Faculty Member Signature and Date

EXHIBIT 2

Materials Considered

Beginning Bates Number	Document
	Opening Expert Report of Jeffrey A. Medin, Ph.D.
	U.S. Patent No. 11,633,388
	U.S. Patent No. 12,042,489
	U.S. Patent No. 12,042,490
	U.S. Patent No. 11,833,164
DEFMIG_0000140	United States Patent Publication Number (“U.S. Pat. Pub. No.”) 2011/0152319 to Benjamin et al (“the ’319 Publication”)
DEFMIG_0000733	U.S. Pat. Pub. No. 2015/0352093 to Lockhart et al. (“Lockhart ’093”)
DEFMIG_0000693	Roberto Giugliani et al., A Phase 2 Study of Migalastat Hydrochloride in Females with Fabry Disease: Selection of Population, Safety and Pharmacodynamic Effects, 109 Molecular Genetics & Metabolism 86 (2013) (“Giugliani”)
DEFMIG_0000640	Dominique Germain et al., <i>Safety and Pharmacodynamic Effects of a Pharmacological Chaperone on α-Galactosidase A Activity and Globotriaosylceramide Clearance in Fabry Disease: Report from Two Phase 2 Clinical Studies</i> , 7 Orphanet J. Rare Diseases 1 (2012) (“Germain 2012”)
DEFMIG_0000583	Elfrida R. Benjamin et al., <i>The Validation of Pharmacogenetics in the Identification of Target Fabry Patients for Treatment of Migalastat</i> , Posters at World Symposium (Mar. 1, 2016) (“Benjamin 2016”)
DEFMIG_0001119	Xiaoyang Wu et al., <i>A Pharmacogenetic Approach to Identify Mutant Forms of α-Galactosidase A that Respond to a Pharmacological Chaperone for Fabry Disease</i> , 32 Hum. Mutation 965 (2011) (“Wu”)
ATGAL_10161649	Platt, F.M., (2018) Lysosomal Storage Diseases, <i>Nat rev Dis Primers</i> 4(1):27
ATGAL_10034456	Germain, D., (2010) Fabry Disease, <i>Orphanet J. of Rare Dis.</i> 5:30
ATGAL_10161508	Gros, F., Muller, S., (2023) The Role of Lysosomes in Metabolic & Autoimmune Diseases, <i>Nature Revs. Nephrology</i> 19:366–83

ATGAL_10161327	Sun, A., (2018) Lysosomal Storage Disease Overview, <i>Ann. Transl. Med.</i> 6(24):476
ATGAL_09818528	Ortiz A., (2018) Fabry disease Revisited: Management and Treatment Recommendations for Adult Patients, <i>Molecular Genetics and Metabolism</i> 123(4): 416–427
ATGAL_07011379	Desnick, R., Ioannou, Y., Eng, C., α -Galactosidase A Deficiency: Fabry Disease, <i>Online Metabolic & Molecular Bases of Inherited Disease</i> (McGraw-Hill Education; 2019)
ATGAL_10161341	Izhar, R. <i>et al.</i> , (2023) Fabry Disease in Women: Genetic Basis, Available Biomarkers, & Clinical Manifestations, <i>Genes</i> 15(1):37
ATGAL_00216964	Lidove, O. <i>et al.</i> , (2016) Fabry in the Older Patient: Clinical Consequences & Possibilities for Treatment, <i>Mol. Genet. Metab.</i> 118(4):319
ATGAL_10161364	Arias, E. <i>et al.</i> , (2022) Provisional Life Expectancy Estimates for 2021, <i>Nat'l Ctr. for Health Stat. Reps.</i> 23
ATGAL_10161380	Anania, M. <i>et al.</i> , (2025) Identification of Four New Mutations in the GLA Gene Associated with Anderson–Fabry Disease, <i>Int. J. Mol. Sci.</i> 26(2):473
ATGAL_00216171	Gal, A., Schafer, E., Rohard, I., The Genetic Basis of Fabry Disease, <i>Fabry Disease: Perspectives from 5 Years of FOS</i> (NCBI Bookshelf; 2006)
ATGAL_07871417	Benjamin, E. <i>et al.</i> , (2017) The Validation of Pharmacogenetics for the Identification of Fabry Patients to be Treated with Migalastat, <i>Genet. Med.</i> 19(4)436
ATGAL_08225720	Wang, R. <i>et al.</i> , (2007) Heterozygous Fabry Women Are Not Just Carriers, But Have a Significant Burden of Disease & Impaired Quality of Life, <i>Genet. Med.</i> 9(1):34–45
ATGAL_10161404	Michaud, M. <i>et al.</i> , (2020) When & How to Diagnose Fabry Disease in Clinical Practice, <i>Am. J. Med. Scis.</i> 360(6):641–49
ATGAL_03927842	Hopkin R.J., (2023) Clinical Outcomes Among Young Patients with Fabry Disease Who Initiated Agalsidase Beta Treatment Before 30 Years of Age: An Analysis from the Fabry Registry, <i>Mol. Genet. Metab.</i> 138(2):10696
ATGAL_10161393	Dutra-Clarke, M. <i>et al.</i> , (2021) Variable Clinical Features of Patients with Fabry Disease & Outcome of Enzyme Replacement Therapy, <i>Mol. Genet. Metab. Reps.</i> 26:100700

ATGAL_10161465	Patient Stories, FSIG, https://fabry.org/patientstories/
ATGAL_05355923	Dec. 14, 2017 Amicus Announcement, Amicus Therapeutics Submits New Drug Application to U.S. FDA for Migalastat for Treatment of Fabry Disease
ATGAL_09880475	Aug. 10, 2018 FDA News Release, FDA Approves New Treatment for a Rare Genetic Disorder, Fabry Disease
ATGAL_06388594	June 2024 GALAFOLD Prescribing Information
ATGAL_10161438	McCafferty, E., Scott, L., (2019) Migalastat: A Review in Fabry Disease, <i>Drugs</i> 79(5):543-54
ATGAL_10036328	Pieroni, M. <i>et al.</i> , (2021) Cardiac Involvement in Fabry Disease, <i>J. Am. Coll. Cardiology</i> 77(7):922–36
ATGAL_04808173	Liguori, L. <i>et al.</i> , (2020) Pharmacological Chaperones: A Therapeutic Approach for Diseases Caused by Destabilizing Missense Mutations, <i>Int. J. Mol. Sci.</i> 21(2):489
ATGAL_01221622	Nov. 6, 2012 FDA Advice/Information Request
ATGAL_01109151	Dec. 19, 2012 Press Release Amicus Therapeutics and GSK Announce Top Line 6-Month Primary Treatment Period Results from First Phase 3 Fabry Monotherapy Study
ATGAL_01433113	June 30, 2009 Fabry Mutagenesis Screening Database
ATGAL_00416643	June 11, 2012 Data Sheet-xw
ATGAL_00730664	Jan Lukas et al., <i>Functional and Clinical Consequences of Novel α-Galactosidase A Mutations in Fabry Disease</i> , Human Mutation, Vol. 00, No. 0, 1–9 (2015)
ATGAL_09916904; ATGAL_01136145	Jan Lukas et al., <i>Functional Characterisation of Alpha-Galactosidase A Mutations as a Basis for a New Classification System in Fabry Disease</i> , PLOS Genetics, Vol 9, Issue 8 (Aug. 2013) and Supplementary Table S1
ATGAL_10161626	Keyzor I., et al., (2023) Therapeutic Role of Pharmacological Chaperones in Lysosomal Storage Disorders: A Review of the Evidence and Informed Approach to Reclassification, <i>Biomolecules</i> 13(8):1227
ATGAL_07336052	May 31, 2016, Amicus Therapeutics Announces European Commission Approval for Galafold™ (Migalastat) in Patients with Fabry Disease in European Union

ATGAL_10161450	Moran, N., (2018) FDA Approves Galafold, a Triumph for Amicus, <i>Nat. Biotech.</i> 36:91
ATGAL_09687616	May 2010 FABRAZYME Prescribing Information
ATGAL_09472479	Oct. 29, 2013 HEK Assay Slides Desnick Visit
ATGAL_09479478	Aug. 7, 2015 GLP HEK Assay Slides for Jeff
	February 6, 2025 Deposition of Elfrida Benjamin

EXHIBIT C

**UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE**

AMICUS THERAPEUTICS US, LLC and
AMICUS THERAPEUTICS, INC.,

Plaintiffs,

v.

TEVA PHARMACEUTICALS USA, INC.
and TEVA PHARMACEUTICALS, INC.,

Defendants.

C.A. No. 22-1461 (CJB)
CONSOLIDATED

**CONFIDENTIAL – SUBJECT TO
PROTECTIVE ORDER**

REPLY REPORT OF JOHN L. JEFFERIES, M.D.

May 23, 2025

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I. INTRODUCTION

1. I previously offered opinions on certain objective indicia of non-obviousness for the Asserted Claims in this litigation in my opening expert report, dated April 4, 2025 (“Opening Report”). Specifically, I opined that (1) there was a long-felt but unmet need for Amicus’s inventions in the Asserted Claims; (2) there were failures of others to solve the problems solved by Amicus’s inventions claimed in the Asserted Claims of the Reassessment Mutations Patents; and (3) there was industry praise for Amicus’s inventions claimed in the Asserted Claims of the Reassessment Mutations Patents. Dr. Medin submitted an expert report responding to my opinions on these objective indicia of non-obviousness. Below, I provide my opinions responding to Dr. Medin’s rebuttal report.

II. SUMMARY OF OPINIONS

2. For the reasons discussed in my Opening Report and in this report, in my opinion, there was a long-felt but unmet need for Amicus’s inventions in the Asserted Claims of the Reassessment Mutations Patents and the Engineered Mutations Patent, there were failures of others to solve the problems solved by Amicus’s inventions claimed in the Asserted Claims of the Reassessment Mutations Patents, and there was industry praise for Amicus’s inventions claimed in the Asserted Claims of the Reassessment Mutations Patents. As I discuss in detail below, I disagree with many of Dr. Medin’s responses to my opinions on these objective indicia of non-obviousness. Nothing in Dr. Medin’s rebuttal report changes the opinions that I rendered in my Opening Report.

III. DOCUMENTS AND MATERIALS CITED

3. In reaching my opinions, I have relied on (i) the documents and materials cited in my Opening Report, including those set forth in Exhibit 2 to my Opening Report, (ii) the Rebuttal Expert Report of Dr. Jeffery A. Medin on Secondary Considerations of Non-

Obviousness and the materials cited in his report, including those listed in Exhibit A to Dr. Medin's report including paragraphs 42–46 of Dr. Medin's Opening Report that he incorporates into his Rebuttal Report, and (iii) any additional materials cited in this report, including those set forth in **Exhibit 1** to this report.

IV. RESPONSE TO DR. MEDIN'S TUTORIAL AND BACKGROUND SECTION

A. Response to Dr. Medin's Criticisms Related to My Characterization of ERT

4. Dr. Medin opines that I have made "multiple assertions regarding prior treatments, but primarily ERT, that are incorrect."¹ I disagree and respond to each of his specific criticisms below.

5. Dr. Medin's main criticism is that ERT was available as a treatment option, that it is still considered safe and effective, and that it was the standard of care at the time of the patented inventions, and therefore there can be no long-felt unmet need for a different type of Fabry treatment.² Although I agree that the ERT treatment³ FABRAZYME was known and used before the May 30, 2017 priority date of the Reassessment Mutations Patents and the August 7,

¹ Medin Rebuttal Report, ¶ 27.

² Medin Rebuttal Report, ¶¶ 28–30, 39–40.

³ To the extent that Dr. Medin uses the term "ERT" to imply there were therapeutics other than FABRAZYME for the treatment of Fabry disease prior to the May 30, 2017 priority date of the Reassessment Mutations Patents and the August 7, 2019 priority date of the Engineered Mutations Patent, I disagree. FABRAZYME was the only approved ERT treatment option in the United States before the May 30, 2017 priority date of the Reassessment Mutations Patents and the August 7, 2019 priority date of the Engineered Mutations Patent. Unless otherwise indicated, ERT refers to FABRAZYME (agalsidase beta) as that was the only ERT treatment for Fabry disease available in the United States at the time of the priority dates used in my analyses. This is true in my Opening Report as well, where I reference ERT available in the United States prior to May 30, 2017 and August 7, 2019. Several years after the priority dates, on May 9, 2023, an additional ERT treatment ELFABRIO (pegunigalsidase alfa-iwxj) was approved by FDA. Another ERT treatment REPLAGAL is under development but is not yet approved in the United States.

2019 priority date of the Engineered Mutations Patent, a single treatment option that is safe and effective for certain patients does not mean that there is not a long-felt but unmet need for alternative treatment options that are safe, effective but also less burdensome and more convenient.⁴ Similarly, just because some patients are treated successfully with FABRAZYME does not mean that all patients will be treated successfully or that treatment with FABRAZYME will continue to be successful. Further, I disagree with Dr. Medin’s suggestion that, because FABRAZYME for Fabry disease “makes substantial amounts of money,” FABRAZYME is satisfying all patients’ needs for treatment.⁵

6. As I describe in my Opening Report and in this report, not every patient can or will agree to FABRAZYME as a treatment option.⁶ Some patients may have difficulty attending frequent, hours-long FABRAZYME infusion treatments and may end up missing treatments due to the significant time commitment for the treatment.⁷ For patients with amenable mutations, an oral treatment option that requires taking a capsule every other day is a life changing treatment option that likely leads to higher patient compliance and better outcomes in slowing the irreversible organ damage caused by Fabry disease.⁸ Further, GALAFOLD is more available in

⁴ See Sections V.A.1, V.B below.

⁵ Medin Rebuttal Report, ¶ 40.

⁶ See Opening Report, ¶¶ 58–62, 87.

⁷ Opening Report, ¶ 59; Berry, L. *et al.*, (2024) Patient-Reported Experience with Fabry Disease & Its Management in the Real-World Setting: Results from a Double-Blind, Cross-Sectional Survey of 280 Respondents, *Orphanet J. Rare Dis.* **19**:153 (ATGAL_10161416 at -423).

⁸ Opening Report, ¶ 69; Moran, N., (2018) FDA Approves Galafold, a Triumph for Amicus, *Nat. Biotech.* **36**:913 (ATGAL_10161450 at -450); Müntze, J. *et al.*, (2023) Patient Reported Quality of Life & Medication Adherence in Fabry Disease Patients Treated with Migalastat: A Prospective, Multicenter Study, *Mol. Genet. Metab.* **138**(2):106981 (ATGAL_03972963 at -963–64).

the body as it can readily diffuse into organs that FABRAZYME and other ERT treatments do not.⁹ [REDACTED]

[REDACTED].¹⁰ As documented in scientific literature, for certain patients FABRAZYME therapy results in adverse events, e.g., infusion-associated reactions or generation of antibodies against FABRAZYME.¹¹ These antibodies, in turn, can affect the efficacy of FABRAZYME and worsen any infusion-associated reactions.¹² Other patients, like adolescent patients, can develop severe needle phobia that prevents them from being treated with ERT.¹³ Further, for any patient, getting an intravenous infusion every other week is unpleasant and can be painful, especially for a repeated treatment where the patient's veins have been used repeatedly for prior infusions. In addition, in a recent survey of European healthcare workers, four out of five who prescribed or administered ERT to adolescent Fabry patients—before

⁹ Opening Report, ¶ 71; Wu, Y. *et al.*, (2021) Migalastat Tissue Distribution: Extrapolation from Mice to Humans Using Pharmacokinetic Modeling & Comparison with Agalsidase Beta Tissue Distribution in Mice, *Clinical Pharmacology Drug Dev.* **10**(9):1075–88 (ATGAL_10161482 at -492).

¹⁰ [REDACTED]

¹¹ Opening Report, ¶¶ 59, 62; Berry, L. *et al.*, (2024) Patient-Reported Experience with Fabry Disease & Its Management in the Real-World Setting: Results from a Double-Blind, Cross-Sectional Survey of 280 Respondents, *Orphanet J. Rare Dis.* **19**:153 (ATGAL_10161416 at -417, -423–26); July 2024 FABRAZYME Prescribing Information (ATGAL_10161430 at -432).

¹² Berry, L. *et al.*, (2024) Patient-Reported Experience with Fabry Disease & Its Management in the Real-World Setting: Results from a Double-Blind, Cross-Sectional Survey of 280 Respondents, *Orphanet J. Rare Dis.* **19**:153 (ATGAL_10161416 at -417); Bashorum, L. *et al.*, (2022) Burden Associated with Fabry Disease and Its Treatment in 12-15 Year Olds: Results from a European Survey, *Orphanet J. Rare Dis.* **17**:266 (ATGAL_06691824 at -825–26).

¹³ Bashorum, L. *et al.*, (2022) Burden Associated with Fabry Disease and Its Treatment in 12-15 Year Olds: Results from a European Survey, *Orphanet J. Rare Dis.* **17**:266 (ATGAL_06691824 at -826).

GALAFOLD was approved for adolescent patients in Europe—stated that there was a “need for more manageable treatment options.”¹⁴ In my practice, about one out of five patients treated with ERT will develop significant side effects where ERT is no longer a viable treatment option or ERT no longer results in a successful outcome.

7. Dr. Medin also opines that my Opening Report statements on ERT imply that a person skilled in the art would not view ERT as a viable treatment option for Fabry patients.¹⁵ I disagree with Dr. Medin’s characterization of my Opening Report. My opinion is that treatment with GALAFOLD is a less burdensome and more effective treatment option for certain Fabry patients.¹⁶ In my opinion, until other therapies are available, ERT is the treatment option for Fabry patients with non-amenable mutations as long as patients respond to ERT.

8. Dr. Medin also disagrees with my statement that “the inability of the artificial enzyme to cross the blood-brain barrier and poor uptake into certain cells limits the utility of ERT in some patients.”¹⁷ In Dr. Medin’s view, the inability of the artificial or recombinant enzyme to cross the blood-brain barrier is not relevant for Fabry patients because “direct central nervous system (CNS) involvement in Fabry disease is rare.”¹⁸ This is inconsistent with scientific literature, which describes the high occurrence of direct CNS involvement in Fabry

¹⁴ Bashorum, L. *et al.*, (2022) Burden Associated with Fabry Disease and Its Treatment in 12-15 Year Olds: Results from a European Survey, *Orphanet J. Rare Dis.* **17**:266 (ATGAL_06691824 at -824).

¹⁵ Medin Rebuttal Report, ¶¶ 38–39.

¹⁶ Opening Report, ¶¶ 65–72.

¹⁷ Medin Rebuttal Report, ¶ 38.

¹⁸ Medin Rebuttal Report, ¶ 38.

disease.¹⁹ Multiple studies describe both direct and indirect CNS involvement in Fabry disease. For example, an article by Drs. Burlina and Politei reports that CNS is extensively involved in Fabry disease and that cerebrovascular findings include strokes and brain vessel abnormalities.²⁰ While many neurologic symptoms such as stroke can be attributed to cerebral vasculopathy, this vascular pathology itself reflects CNS-relevant disease mechanisms that are poorly treated by ERT due to its inability to cross the blood-brain barrier.²¹ For example, a book chapter by Drs. Schiffman and Moore reports that the primary neurological manifestations of Fabry disease include cerebral vasculopathy that results in a markedly increased risk of stroke and contributes significantly to morbidity and mortality in Fabry patients.²² Further, Dr. Sims and her colleagues report cerebrovascular complications caused by cerebral vasculopathy as a source of disease

¹⁹ See Schiffmann, R., Moore, D.F., *Neurological Manifestations of Fabry Disease*, Fabry Disease: Perspectives from 5 Years of FOS (NCBI Bookshelf; 2006) (ATGAL_10161840 at -840); Burlina, A., Politei, J., (2016) The Central Nervous System Involvement in Fabry Disease: A Review, *J. of Inborn Errors of Metabolism and Screening* 4:1–7 (ATGAL_09818936 at -936–38, -940); Sims, K. *et al.*, (2009) Stroke in Fabry Disease Frequently Occurs Before Diagnosis and in the Absence of Other Clinical Events: Natural History Data from the Fabry Registry, *Stroke* 40(3):788–94 (ATGAL_09879249 at -249).

²⁰ Burlina, A., Politei, J., (2016) The Central Nervous System Involvement in Fabry Disease: A Review, *Journal of Inborn Errors of Metabolism and Screening* 4:1–7 (ATGAL_09818936 at -936–38, -940).

²¹ See Burlina, A., Politei, J., (2016) The Central Nervous System Involvement in Fabry Disease: A Review, *Journal of Inborn Errors of Metabolism and Screening* 4:1–7 (ATGAL_09818936 at -940).

²² See Schiffmann, R., Moore, D.F., *Neurological Manifestations of Fabry Disease*, Fabry Disease: Perspectives from 5 Years of FOS (NCBI Bookshelf; 2006) (ATGAL_10161840 at -840).

burden and early death.²³ In addition, sleep apnea, fatigue, depression, and anxiety in Fabry patients also indicate direct CNS involvement.²⁴

9. Further, there is also growing evidence of primary CNS involvement, including cognitive impairment, white matter lesions, and Fabry-associated depression—findings not solely attributable to systemic vascular disease. An article by Drs. Burlina and Politei highlights extensive CNS manifestations and structural brain abnormalities in Fabry patients, indicating a more direct involvement of the CNS itself.²⁵ These manifestations are unlikely to be effectively treated with ERT, which does not reach the brain, and may instead require agents like migalastat (GALAFOLD), which crosses the blood-brain barrier and may provide therapeutic benefit within the CNS. Thus, the exclusion of CNS considerations in Fabry management underestimates both the complexity of the disease and the potential value of blood-brain-barrier-penetrant therapies.

B. Response to Dr. Medin's Criticisms on My Comparison of GALAFOLD and ERT and FDA Approval of GALAFOLD

10. Below is my response to Dr. Medin's criticisms on the background section of my Opening Report related to different treatments of Fabry disease and FDA approval of GALAFOLD. While responding to Dr. Medin's criticisms, I grouped my response to Dr.

²³ Sims, K. *et al.*, (2009) Stroke in Farby Disease Frequently Occurs Before Diagnosis and in the Absence of Other Clinical Events, *Stroke* **40**(3):788–94 (ATGAL_09879249 at -249, -252–54).

²⁴ Blaszczyk, B. *et al.*, (2023) Fabry Disease and Sleep Disorders: A Systematic Review, *Front. Neurol.* **14**:1217618 (ATGAL_10161694 at -694); Müller, M., Neuropsychiatric and Psychosocial Aspects of Fabry Disease, *Fabry Disease: Perspectives from 5 Years of FOS* (NCBI Bookshelf; 2006) (ATGAL_10161704 at -704, -707–09); Gambardella, J. *et al.*, (2024) Fatigue as Hallmark of Fabry Disease: Role of Bioenergetic Alterations, *Front. Cardiovasc. Med.* **11**:1341590 (ATGAL_10161722 at -722–24).

²⁵ Burlina, A., Politei, J., (2016) The Central Nervous System Involvement in Fabry Disease: A Review, *J. of Inborn Errors of Metabolism and Screening* **4**:1–7 (ATGAL_09818936 at -936–40).

Medin's opinions on various subject matters rather than responding to his criticisms in the order they appear in Dr. Medin's Rebuttal Report.

11. Dr. Medin claims that I suggest that "early and accurate diagnosis of Fabry disease is the key, not the actual treatment."²⁶ This is incorrect. In my Opening Report, I explain that while there are effective treatments like GALAFOLD and ERT available for Fabry patients, diagnosis of Fabry disease when it first starts becoming symptomatic followed by treatment without delay is the key to minimize organ damage.²⁷ In my experience and that of other doctors who diagnose and treat Fabry patients regularly, reliable diagnosis of Fabry disease can be challenging because (1) Fabry disease presents with variable symptoms and (2) it is an X-linked disease, making it more challenging to diagnose, especially for patients with non-classical Fabry and for female patients.²⁸

12. With respect to treatment with GALAFOLD, Dr. Medin opines that "the concept of 'amenable' is an arbitrarily assigned term based on other LSDs and perceived changes in enzyme activity needed for correction in Fabry disease and this arbitrariness, as a [person of ordinary skill in the art] would understand, is why migalastat does not work for some patients who have so-called amenable mutations."²⁹ I disagree. The term "amenable" in the Asserted Claims and the GALAFOLD product label is not arbitrary. Amenability is defined in the Asserted Patents as "showing a relative increase (+10 μ M migalastat) of ≥ 1.20 -fold and an

²⁶ Medin Rebuttal Report, ¶ 28.

²⁷ See Opening Report, ¶ 48 ("Recognition of Fabry disease is important because effective treatments are available, but they have to be prescribed early in the disease to be more effective in preventing organ damage.").

²⁸ Opening Report, ¶ 48.

²⁹ Medin Rebuttal Report, ¶ 37.

absolute increase (+10 μ M migalastat) of $\geq 3.0\%$ wild-type when the mutant form of α -galactosidase A is expressed.”³⁰ Through the Migalastat Amenability Assay, Amicus scientists determined which α -GAL A mutant enzymes would respond to migalastat so that the defective enzymatic activity would be increased by the interaction of the enzyme and migalastat. Further, when migalastat is administered to such patients, Amicus found that the patients generally respond favorably and Amicus saw a tight correlation between amenability as defined by the Asserted Patents and favorable clinical outcomes.³¹

13. Dr. Medin also opines that “migalastat does not work for some patients who have so-called amenable mutations.”³² It is not entirely clear what Dr. Medin means, but in my opinion, a single treatment option is generally not sufficient for treating any population of patients, including the population of Fabry patients with amenable mutations. Within the population of amenable Fabry patients, there are a small subset of patients for whom GALAFOLD is not the ideal treatment option, because, as I describe in my Opening Report, symptoms of Fabry disease vary between patients and sometimes the disease progresses too far, or a patient has other comorbidities or other contributing factors that make GALAFOLD less effective as a treatment option for that particular patient.³³

³⁰ '388 Patent, col.17:7–15; '489 Patent, col.17:30–37; '490 Patent, col.17:28–35; '164 Patent, col.26:1–9.

³¹ Benjamin, E. *et al.*, (2017) The Validation of Pharmacogenetics for the Identification of Fabry Patients to be Treated with Migalastat, *Genet. Med.* **19**(4):430–38 (ATGAL_07871417 at -423–24).

³² Medin Rebuttal Report, ¶ 37.

³³ See Opening Report, ¶¶ 48, 49.

14. Next, Dr. Medin criticizes my statement that cells of the heart and kidney take up limited amounts of recombinant enzyme.³⁴ According to Dr. Medin, these organs are composed of different cell types and in clinical trials ERT led to a reduced rate of renal and cardiac clinical events.³⁵ While ERT does have some positive effects on renal and cardiac events, the literature shows that GALAFOLD has a greater effect.³⁶ For example, Dr. Riccio reported that migalastat significantly reduced cardiac mass compared with ERT in Fabry patients.³⁷ In a study done in Italy, seven Fabry disease patients with amenable mutations were treated with ERT for one year and then they were switched to GALAFOLD without any interval.³⁸ After one year of being

³⁴ Medin Rebuttal Report, ¶ 44.

³⁵ Medin Rebuttal Report, ¶ 44.

³⁶ See, e.g., McCafferty, E., Scott, L., (2019) Migalastat: A Review in Fabry Disease, *Drugs* **79**(5):543–54 (ATGAL_10161438 at -438); Riccio, E. *et al.*, (2020) Switch from Enzyme Replacement Therapy to Oral Chaperone Migalastat for Treating Fabry Disease: Real-Life Data, *Eur. J. of Hum. Genetics* **28**:1662–68 (ATGAL_08508336 at -336); Nowicki, M. *et al.*, (2024) A Review and Recommendations for Oral Chaperone Therapy in Adult Patients with Fabry Disease, *Orphanet J. Rare Dis.* **19**:16 (ATGAL_10161856 at -859–80); see also Amicus Therapeutics Announces Positive Phase 3 Data on Cardiac and Composite Endpoints from Fabry Monotherapy Study 012 at American Society of Nephrology, *Pipeline Review* (Nov. 17, 2014), <https://pipelinereview.com/amicus-therapeutics-announces-positive-phase-3-data-on-cardiac-and-composite-endpoints-from-fabry-monotherapy-study-012-at-american-society-of-nephrology> (ATGAL_10161674 at -674); Lenders, M. *et al.*, (2016) Serum-Mediated Inhibition of Enzyme Replacement Therapy in Fabry Disease, *J. Am. Soc. Nephrol.* **27**:256–64 (ATGAL_06866922 at -926–28); Alegra, T. *et al.*, (2012) Enzyme Replacement Therapy for Fabry Disease: A Systematic Review and Meta-Analysis, *Genet. Mol. Biol.* **35**(4 supp.):947–54 (ATGAL_08454411 at -415–17); Hendriksz, C.J. *et al.*, (2018) Risks of Long-Term Port Use in Enzyme Replacement Therapy for Lysosomal Storage Disorders, *Mol. Genet. Metab. Reps.* **15**:71–73 (ATGAL_10161730 at -730–32).

³⁷ Riccio, E. *et al.*, (2020) Switch from Enzyme Replacement Therapy to Oral Chaperone Migalastat for Treating Fabry Disease: Real-Life Data, *Eur. J. of Hum. Genetics* **28**:1662–68 (ATGAL_08508336 at -336).

³⁸ Riccio, E. *et al.*, (2020) Switch from Enzyme Replacement Therapy to Oral Chaperone Migalastat for Treating Fabry Disease: Real-Life Data, *Eur. J. of Hum. Genetics* **28**:1662–68 (ATGAL_08508336 at -336–37).

treated with GALAFOLD, clinical assessment on these patients showed that the left ventricular mass index (a measure of heart size) and protein levels in their urine (a marker of kidney dysfunction) were reduced significantly compared to the values obtained while these patients were on ERT.³⁹

15. Dr. Medin disagrees with my statement that the recombinant enzyme in ERTs such as FABRAZYME is not taken up by all the organs, but rather in a subset of organs.⁴⁰ My opinion is that migalastat readily diffuses into most cells and tissues unlike the recombinant enzyme in ERTs such as FABRAZYME.⁴¹ Scientific literature that Dr. Medin cites is not applicable to my statement because those papers discuss only the localization of the recombinant enzyme and does not discuss migalastat.⁴² The three cited papers were published in 2001 and 2006, well before the priority dates here, and do not address how migalastat is distributed.⁴³ I

³⁹ Riccio, E. *et al.*, (2020) Switch from Enzyme Replacement Therapy to Oral Chaperone Migalastat for Treating Fabry Disease: Real-Life Data, *Eur. J. of Hum. Genetics* **28**:1662–68 (ATGAL_08508336 at -336).

⁴⁰ Medin Rebuttal Report, ¶ 46.

⁴¹ Opening Report, ¶ 71.

⁴² Medin Rebuttal Report, ¶ 46 (citing Eng, C. *et al.*, (2001) Safety and Efficacy of Recombinant Human Alpha-Galactosidase a Replacement Therapy in Fabry's Disease, *N. Engl. J. Med.* **345**(1):9–16 (AURO_MEDIN_000269 at -269); Eng, C. *et al.*, (2001) A Phase 1/2 Clinical Trial of Enzyme Replacement in Fabry Disease: Pharmacokinetic, Substrate Clearance, and Safety Studies, *Am. J. Hum. Genetics* **68**(3):711–22 (AURO_MEDIN_000277 at -277); Murray, G. J. *et al.*, (2007) Cellular and Tissue Distribution of Intravenously Administered Agalsidase Alfa, *Mol. Genet. Metab.* **90**(3):307–12 (AURO_MEDIN_000289 at -289)).

⁴³ Eng, C. *et al.*, (2001) Safety and Efficacy of Recombinant Human Alpha-Galactosidase A Replacement Therapy in Fabry's Disease, *N. Engl. J. Med.* **345**(1):9–16 (AURO_MEDIN_000269 at -269); Eng, C. *et al.*, (2001) A Phase 1/2 Clinical Trial of Enzyme Replacement in Fabry Disease: Pharmacokinetic, Substrate Clearance, and Safety Studies, *Am. J. Hum. Genet.* **68**(3):711–22 (AURO_MEDIN_000277 at -277); Murray, G. J., *et al.*, (2007) Cellular and Tissue Distribution of Intravenously Administered Agalsidase Alfa, *Mol. Genet. Metab.* **90**(3), 307–12 (AURO_MEDIN_000289 at -289).

note that Dr. Medin does not dispute my statement that migalastat readily diffuses into most cells and tissues.⁴⁴

16. Dr. Medin criticizes my statement about podocytes being “relatively ERT-resistant” and opines that ERT has been shown to reduce GL-3 in podocytes.⁴⁵ But podocytes are relatively poor responders to ERT, a fact that is confirmed by the references cited by Dr. Medin.⁴⁶ For example, the Najafian article states: “While enzyme replacement therapy (ERT) eliminates visible GL3 accumulation in kidney endothelial and mesangial cells and fibroblasts within 5 months, podocytes . . . are more resistant to ERT.”⁴⁷ In fact, podocytes are considered an ERT-resistant cell type and the Najafian article confirms my opinion that “the incomplete effects of ERT on podocyte GL3 provides opportunities for testing the value of new treatments to supplement ERT.”⁴⁸

⁴⁴ See Wu, Y. *et al.*, (2021) Migalastat Tissue Distribution: Extrapolation from Mice to Humans Using Pharmacokinetic Modeling & Comparison with Agalsidase Beta Tissue Distribution in Mice, *Clinical Pharmacology Drug Dev.* **10**(9):1075–88 (ATGAL_10161482 at -492); *see also* June 2024 GALAFOLD Prescribing Information (ATGAL_06388594 at -614).

⁴⁵ Medin Rebuttal Report, ¶ 47.

⁴⁶ Medin Rebuttal Report, ¶ 47 (citing Najafian, B. *et al.*, (2016) One Year of Enzyme Replacement Therapy Reduces Globotriaosylceramide Inclusions in Podocytes in Male Adult Patients with Fabry Disease, *PLoS ONE* **11**(4):e0152812 (AURO_MEDIN_000304 at -304)).

⁴⁷ Najafian, B. *et al.*, (2016) One Year of Enzyme Replacement Therapy Reduces Globotriaosylceramide Inclusions in Podocytes in Male Adult Patients with Fabry Disease, *PLoS ONE* **11**(4):e0152812 (internal citations omitted) (AURO_MEDIN_000304 at -304).

⁴⁸ Najafian, B. *et al.*, (2016) One Year of Enzyme Replacement Therapy Reduces Globotriaosylceramide Inclusions in Podocytes in Male Adult Patients with Fabry Disease, *PLoS ONE* **11**(4):e0152812 (internal citations omitted) (AURO_MEDIN_000304 at -314).

17. Dr. Medin also opines that “migalastat can produce antibodies.”⁴⁹ Notably, Dr. Medin does not cite any evidence that migalastat has been shown to produce antibodies and instead simply infers it may be possible because migalastat is “a foreign substance in humans” and because some carbohydrates may engender antibody production.⁵⁰ The literature, however, does not support such an inference.⁵¹ There have been no reported anti-migalastat antibodies in patients treated with GALAFOLD and migalastat is considered non-immunogenic.⁵² In contrast, as I have described in my Opening Report and in this report, neutralizing antidrug antibodies have been reported in Fabry patients treated with ERT.⁵³

18. Dr. Medin also alleges that “migalastat was not the miracle drug or solution” relying on several terminated clinical studies and other clinical studies where the results were not posted on clinicaltrials.gov.⁵⁴ I do not agree that in general failures in clinical trials reflect that no long-felt need exists and I do not agree that all clinical trials listed by Dr. Medin are failures. Based on my experience as a medical doctor who has conducted clinical trials for rare diseases, it is common to terminate trials or not to post results where there are not enough participants to reach a statistically significant conclusion on safety, efficacy, or other endpoints. It is common for investigators to have issues enrolling enough patients for clinical studies on rare diseases

⁴⁹ Medin Rebuttal Report, ¶ 45.

⁵⁰ Medin Rebuttal Report, ¶ 45.

⁵¹ E.g., McCafferty, E., Scott, L., (2019) Migalastat: A Review in Fabry Disease, *Drugs* 79(5):543–54 (ATGAL_10161438 at -446).

⁵² See McCafferty, E., Scott, L., (2019) Migalastat: A Review in Fabry Disease, *Drugs* 79(5):543–54 (ATGAL_10161438 at -446).

⁵³ Opening Report, ¶ 62.

⁵⁴ Medin Rebuttal Report, ¶¶ 57–58.

because of the small patient populations.⁵⁵ It is also common to terminate such studies if it becomes apparent that no statistical conclusion may be reached because clinical trials are expensive and small companies do not have the means to support trials that will not result in meaningful results.

19. Further, Dr. Medin lists the following studies as examples of studies being terminated for failure to meet their end points, but Dr. Medin ignores specific reasons why these studies were either terminated or no results were published. In addition, I disagree with Dr. Medin that these studies were failures as I describe each in detail below:

- NCT01458119
- 

⁵⁵ See, e.g., Rees, C. A. *et al.*, (2019) Noncompletion and Nonpublication of Trials Studying Rare Diseases: A Cross-Sectional Analysis, *PLoS Med.* **16**(11):e1002966 (ATGAL_10161911 at -911–12); Study to Evaluate Ecallantide in Paediatric Patients with Acute Attacks of Hereditary Angioedema, ClinicalTrials.gov, <https://clinicaltrials.gov/study/NCT01253382> (no results report for angioedema) (ATGAL_10161809 at -809, -814–15); Safety and Efficacy of QAX576 in Patients with Idiopathic Pulmonary Fibrosis (IPF), ClinicalTrials.gov, <https://clinicaltrials.gov/study/NCT01266135> (no results reported for pulmonary fibrosis) (ATGAL_10161817 at -817, -824–25).

⁵⁶ Feb. 15, 2017, Clinical Study Report AT1001-041 (ATGAL_03872004–092 at -022).

⁵⁷ Feb. 15, 2017, Clinical Study Report AT1001-041 (ATGAL_03872004–092 at -090).

⁵⁸ Feb. 15, 2017, Clinical Study Report AT1001-041 (ATGAL_03872004–092 at -082).

⁵⁹ Feb. 15, 2017, Clinical Study Report AT1001-041 (ATGAL_03872004–092 at -088).

[REDACTED] The results were posted on clinicaltrials.gov.⁷¹

- NCT00283959 [REDACTED]

The results were posted on clinicaltrials.gov.⁷⁶

- NCT00214500 [REDACTED]

⁷⁰ June 20, 2011, Clinical Study Report AT1001-FAB-CL-203 (ATGAL_00097754–832 at -831).

⁷¹ A 24-Week Safety and Pharmacodynamic Study of AT1001 (Migalastat Hydrochloride) in Participants with Fabry Disease, ClinicalTrials.gov, <https://clinicaltrials.gov/study/NCT00283933> (ATGAL_10161764 at -771).

⁷² Sept. 13, 2011, Clinical Study Report AT1001-FAB-CL-202 (ATGAL_00096062–137 at -134).

⁷³ Sept. 13, 2011, Clinical Study Report AT1001-FAB-CL-202 (ATGAL_00096062–137 at -134).

⁷⁴ Sept. 13, 2011, Clinical Study Report AT1001-FAB-CL-202 (ATGAL_00096062–137 at -134).

⁷⁵ Sept. 13, 2011, Clinical Study Report AT1001-FAB-CL-202 (ATGAL_00096062–137 at -127).

⁷⁶ A 12-Week Safety and Pharmacodynamic Study of AT1001 (Migalastat Hydrochloride) in Participants with Fabry Disease, ClinicalTrials.gov, <https://clinicaltrials.gov/study/NCT00283959> (ATGAL_10161774 at -781).

⁷⁷ Sept. 8, 2010, Clinical Study Report AT1001-FAB-CL-201 (ATGAL_00092978–3067 at -3064).

⁷⁸ Sept. 8, 2010, Clinical Study Report AT1001-FAB-CL-201 (ATGAL_00092978–3067 at -3064).

⁷⁹ Sept. 8, 2010, Clinical Study Report AT1001-FAB-CL-201 (ATGAL_00092978–3067 at -3064).

- [REDACTED] Results were posted on clinicaltrials.gov.⁸¹
- NCT00925301 was the Study 011 I discussed in my Opening Report where initially there was not a significant difference between the group receiving GALAFOLD and the group receiving placebo.⁸² Results were published in multiple articles and posted on clinicaltrials.gov.⁸³

- NCT02082327 [REDACTED]

- NCT01730469 [REDACTED]

⁸⁰ Sept. 8, 2010, Clinical Study Report AT1001-FAB-CL-201 (ATGAL_00092978–3067 at -3064).

⁸¹ A Study of AT1001 (Migalastat Hydrochloride) in Participants with Fabry Disease, ClinicalTrials.gov, <https://clinicaltrials.gov/study/NCT00214500> (ATGAL_10161752 at -761).

⁸² Opening Report, ¶¶ 81, 85–86.

⁸³ Germain, D. *et al.*, (2019) Efficacy of the Pharmacologic Chaperone Migalastat in a Subset of Male Patients with the Classic Phenotype of Fabry Disease and Migalastat-Amenable Variants: Data from the Phase 3 Randomized, Multicenter, Double-Blind Clinical Trial and Extension Study, *Genet. Med.* **21**(9):1987–97 (ATGAL_09877685 at -685–86); Schiffmann, R. *et al.*, (2018), Migalastat Improves Diarrhea in Patients with Fabry Disease: Clinical-Biomarker Correlations from the Phase 3 FACETS Trial, *Orphanet J. Rare Dis.* **13**(1):68 (ATGAL_07915907 at -907); Bichet, D. *et al.*, (2021) Assessment of Plasma Lyso-Gb3 for Clinical Monitoring of Treatment Response in Migalastat-Treated Patients with Fabry Disease, *Genet. Med.* **23**(1):192–201 (ATGAL_10023551 at -551–52); Study of the Effects of Oral AT1001 (Migalastat Hydrochloride) in Patients with Fabry Disease, ClinicalTrials.gov, <https://clinicaltrials.gov/study/NCT00925301> (ATGAL_10161794 at -807).

⁸⁴ Oct. 7, 2014, Clinical Study Report AT1001-018 (ATGAL_00047810–907 at -823).

⁸⁵ Oct. 7, 2014, Clinical Study Report AT1001-018 (ATGAL_00047810–907 at -877).

⁸⁶ Dec. 5, 2013, Amended Clinical Study Report AT1001-015 (ATGAL_00076781–877 at -844).

⁸⁷ Dec. 5, 2013, Amended Clinical Study Report AT1001-015 (ATGAL_00076781–877 at -845).

- NCT01730482 [REDACTED]

20. Dr. Medin further opines that my statements on GALAFOLD's accelerated approval lack "specificity of what the unmet medical need is and how specifically this relates the specific claims of the patents asserted in this case."⁹⁰ I disagree. My opinion that there was a long-felt but unmet need for Fabry patients with certain mutations, i.e., patients with amenable mutations including those set forth in the Asserted Claims, as described in my Opening Report and in this report, is supported by FDA's recognition of this long-felt but unmet need when it approved GALAFOLD under the accelerated approval program.⁹¹ [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] FDA's standard for accelerated approval, which states, "FDA may approve drugs for serious conditions where there is an unmet medical need and where a drug is shown to have certain effects that are reasonably likely to predict a clinical

⁸⁸ Dec. 11, 2012, Clinical Study Report AT1001-014 (ATGAL_03366897-992 at -947-48).

⁸⁹ Dec. 11, 2012, Clinical Study Report AT1001-014 (ATGAL_03366897-992 at -948).

⁹⁰ Medin Rebuttal Report, ¶ 31; *see* Medin Rebuttal Report, ¶¶ 34-35.

⁹¹ *See, e.g.*, Opening Report, ¶¶ 60-61; Apr. 19, 2017 Amicus Briefing Document to FDA (ATGAL_03771237 at -305-07).

⁹² [REDACTED]

benefit to patients.”⁹³ In contrast, Dr. Medin ignores that this long-felt but unmet need existed for all Fabry patients with amenable mutations including the mutations in the Asserted Claims in this case.⁹⁴

21. Dr. Medin also opines that because the Reassessment Mutations Patents had not issued and the Engineering Mutations Patent was not filed when GALAFOLD was approved, he finds it hard to imagine how long-felt but unmet need statements related to FDA submission might be relevant.⁹⁵ In my opinion, statements on any long-felt but unmet need for an alternative treatment are routinely expressed before a solution is known and even before work to develop alternative treatments is initiated. For example, side effects or other treatment limitations are often identified and later lead to development of new treatments.

V. RESPONSE TO DR. MEDIN REGARDING OBJECTIVE INDICIA SUPPORTING NON-OBVIOUSNESS

22. As discussed in my Opening Report, in my opinion, there was a long-felt but unmet need for Amicus’s inventions in the Asserted Claims of the Reassessment Mutations Patents and the Engineered Mutations Patent, there were failures of others to solve the problem solved by Amicus’s inventions claimed in the Asserted Claims of the Reassessment Mutations Patents, and there was industry praise for Amicus’s inventions claimed in the Asserted Claims of the Reassessment Mutations Patents.⁹⁶ As I discuss in detail below, I disagree with many of

⁹³ Aug. 10, 2018 FDA News Release, FDA Approves New Treatment for a Rare Genetic Disorder, Fabry Disease (ATGAL_09880475 at -476).

⁹⁴ Medin Rebuttal Report, ¶ 31; *see* Medin Rebuttal Report, ¶¶ 34–35.

⁹⁵ Medin Rebuttal Report, ¶ 33.

⁹⁶ Opening Report, ¶¶ 5–7.

Dr. Medin's responses to my opinions on these objective indicia of non-obviousness. Nothing in Dr. Medin's rebuttal report changes the opinions that I rendered in my Opening Report.

A. Long-Felt But Unmet Need

23. In my Opening Report, I opined that the objective indicia of non-obviousness of the Asserted Claims of the Reassessment Mutations Patents and the Engineered Mutations Patent is supported by the fact that GALAFOLD fulfilled a long-felt but unmet need for an improved therapy for Fabry patients with amenable mutations including the claimed mutations.⁹⁷ I discussed how the ERT treatment FABRAZYME was the only FDA-approved treatment for Fabry patients until the approval of GALAFOLD and how FABRAZYME had various drawbacks as a treatment option including being burdensome both for patients and caretakers, generation of antibodies against the recombinant enzyme leading to infusion reactions and diminished efficacy, and the inability of the recombinant enzyme to cross the blood-brain barrier and poor uptake into certain cells limiting the utility of FABRAZYME in some patients.⁹⁸

24. In his rebuttal report, Dr. Medin opines that there is no evidence of a long-felt unmet need for Fabry patients for three reasons: (1) there can be no long-felt unmet need because ERT is the first-line therapy; (2) there is no long-felt unmet need because migalastat treats only some Fabry patients; (3) there is no connection between the long-felt unmet need and the Asserted Claims of the Reassessment Mutations Patents and the Engineered Mutations Patent.⁹⁹ As set forth below, I disagree that there is no evidence of a long-felt unmet need for Fabry

⁹⁷ Opening Report, § XI.A.

⁹⁸ Opening Report, ¶¶ 56–64.

⁹⁹ Medin Rebuttal Report, § VII.A.

patients with amenable mutations and, in my opinion, the reasons Dr. Medin relies on are inapplicable.

1. Even Though ERT Is a First-Line Therapy, There Was a Long-Felt But Unmet Need for Alternative Treatments

25. Dr. Medin opines that the fact that ERT is a first-line therapy “seriously undermines any assertion that migalastat addresses a long-felt unmet need.”¹⁰⁰ I disagree. Dr. Medin is not a clinician and as such he does not diagnose patients as having Fabry disease, determine the appropriate treatment for any Fabry patients, or treat such patients. Despite not having this experience, he opines there was no need to develop an alternative treatment for Fabry disease because there was already a single, safe and effective treatment option.¹⁰¹ Based on my experience as a physician, medical doctors who treat Fabry patients would not agree. A single treatment option, no matter how safe and effective, does not meet the needs of every single patient; Fabry patients are no different. For example, there are many available medications for migraines.¹⁰² Under Dr. Medin’s logic, once the first migraine medication, ergotamine, became available as an effective medication in 1926, there was no need for alternative medications, like triptans, to be developed in 1990 to 2000.¹⁰³ However, in 2008, the American Headache Society

¹⁰⁰ Medin Rebuttal Report, ¶ 64; *see* Medin Rebuttal Report, ¶ 78.

¹⁰¹ Medin Rebuttal Report ¶¶ 64–66.

¹⁰² Peters, G. L., (2019) Migraine Overview and Summary of Current and Emerging Treatment Options, *Am. J. Manag. Care* **25**(2 Suppl):S23–S34 (ATGAL_10161869 at -883–96).

¹⁰³ Elizabeth Pratt, How Migraine Treatments Have Changed Over Time, *Med. News Today* (Sept. 12, 2024), <https://www.medicalnewstoday.com/articles/migraine-treatments-history> (ATGAL_10161927 at -928–30).

declared that triptans are the most important breakthrough in headache medication in 50 years.¹⁰⁴ According to Dr. Medin's approach to treatment development, there was no need for alternative treatments because ergotamine existed and is still used today. In my opinion, Dr. Medin's view that a single treatment option is sufficient to satisfy all long-felt needs for a disease is not shared by the medical community.

26. Dr. Medin further opines that because I do not allege that ERT treatments like FABRAZYME are not safe or effective, a person skilled in the art would not agree that "this is [] demonstration of migalastat filling a long-felt unmet need."¹⁰⁵ I disagree. As discussed in my Opening Report and here, although FABRAZYME is a safe and effective treatment option for certain Fabry patients, it is not suitable for every patient and is associated with significant burdens on both the patients and caregivers.¹⁰⁶ Migalastat fulfilled a long-felt need for an alternative treatment option to FABRAZYME's ERT for a significant number of Fabry patients. Moreover, as I have described extensively in my Opening Report, migalastat is a more convenient treatment option for certain Fabry patients, a fact that is well-documented in the literature.¹⁰⁷ Dr. Medin does not appear to dispute this, but instead opines a single treatment

¹⁰⁴ Humphrey, P.P.A., (2008) The Discovery and Development of the Triptans, a Major Therapeutic Breakthrough, *Headache* **48**:685–87 (ATGAL_10161733 at -733).

¹⁰⁵ Medin Rebuttal Report, ¶¶ 65–66; *see* Medin Rebuttal Report, ¶ 78.

¹⁰⁶ Opening Report, ¶¶ 59–62.

¹⁰⁷ Opening Report, ¶¶ 65–69; Riccio, E. *et al.*, (2020) Switch from Enzyme Replacement Therapy to Oral Chaperone Migalastat for Treating Fabry Disease: Real-Life Data, *Eur. J. of Hum. Genet.* **28**:1662–68 (ATGAL_08508336 at -339–40).

option eliminates the need for any alternative treatments.¹⁰⁸ For the reasons discussed above, I disagree.

27. I have first-hand experience seeing how migalastat has improved the lives of Fabry patients who could not tolerate ERT, did not respond well to ERT, or found the inconvenience of ERT to hinder their personal and professional endeavors. Further, at least in my practice, about one out of every five patients who are treated by ERT develop a side effect where ERT cannot be administered to them or have progression of the disease with ERT. For example, certain of my patients on ERT continued to have progression of cardiac disease despite the ERT treatments.

28. To support his position, Dr. Medin also seems to equate how patients are reimbursed for costs of ERT and migalastat in Australia and cites an article on ERT and how only ERT is reimbursed in Singapore as evidence that ERT meets the needs of every Fabry patient.¹⁰⁹ As a preliminary matter, the article on how Singapore reimburses ERT treatment for Fabry patients is solely focused on ERT, specifically how only agalsidase alpha is reimbursed rather both agalsidase alpha and beta, and does not discuss any other treatment option. I do not agree that drug reimbursement in Australia or Singapore are relevant to my opinion. In my opinion, how patients are reimbursed for costs of a drug or how a chaperone-based therapy is not mentioned in an article on ERT and its reimbursement does not address whether there was a long-felt but unmet need for alternative treatments to ERT in the United States.

¹⁰⁸ Medin Rebuttal Report, ¶¶ 64–66.

¹⁰⁹ Medin Rebuttal Report, ¶ 64.

2. Migalastat Treats Fabry Patients with Amenable Mutations Fulfilling a Long-Felt But Unmet Need for These Patients

29. Dr. Medin opines that because GALAFOLD “[t]reats a [m]inority of Fabry [p]atients,” it does not fulfill a long-felt but unmet need for Fabry patients.¹¹⁰ I disagree. My opinion is that GALAFOLD fulfilled a long-felt but unmet need for a majority of Fabry patients with amenable mutations rather than GALAFOLD fulfilling a long-felt but unmet need for all Fabry patients including the patients with non-amenable mutations. As I have described in my Opening Report, there are different types of mutations and for Fabry patients with certain mutations, migalastat will have no effect; those patients with such non-amenable mutations are not at issue here.¹¹¹

30. Dr. Medin further opines that because by his calculation, “the claimed subject matter [] works for approximately 9% of all Fabry disease patients known at that time,” it does not meet a long-felt unmet need for a method of treating Fabry disease.¹¹² Dr. Medin opines that “no [person of ordinary skill] would agree” there was a long-felt unmet need for the claimed inventions.¹¹³ I disagree with these opinions.

31. As a preliminary matter, Dr. Medin’s “9%” number is irrelevant as there can be a long-felt but unmet need for Fabry patients with certain mutations. Even if it were relevant, Dr. Medin’s calculation is unreliable because he *assumes* that as of 2016, there were at least 600 HEK assay amenable Fabry mutations and then divides 600 by the 56 mutations in the Asserted

¹¹⁰ Medin Rebuttal Report, ¶¶ 67–73.

¹¹¹ Opening Report, ¶¶ 47–49, 53.

¹¹² Medin Rebuttal Report, ¶¶ 43, 73.

¹¹³ Medin Rebuttal Report, ¶ 73.

Claims of the Asserted Patents to arrive at 9%.¹¹⁴ Dr. Medin contradicts himself within his rebuttal report by stating that “as of 2016, there were known approximately 256 amenable mutations,” while also stating that “as of 2016 there were at least 600 HEK assay amenable mutations known.”¹¹⁵

32. Further, Dr. Medin conflates the percentage of α -GAL A mutations with the percentage of Fabry patients.¹¹⁶ Just because Dr. Medin estimates 56 mutations disclosed in the Asserted Claims to be 9.3% of the known α -GAL A mutations or 21.9% of the known amenable mutations in 2016 does not mean that 9% of the Fabry patients have these 56 mutations.¹¹⁷ Some mutations are more prevalent than others.

33. It is undisputed that GALAFOLD can be used to treat the majority of Fabry patients with amenable mutations.¹¹⁸ Even Dr. Medin does not dispute this statement when he states that I base my opinions “on a general acceptance of migalastat to treat amenable mutations.”¹¹⁹ For treatment of Fabry disease, some patients prefer GALAFOLD over ERT because of the need for intravenous access, accessibility, burden on patients’ and caregivers’

¹¹⁴ Medin Rebuttal Report, ¶¶ 68–69.

¹¹⁵ Medin Rebuttal Report, ¶¶ 67–68.

¹¹⁶ Medin Rebuttal Report, ¶¶ 67–73.

¹¹⁷ See Medin Rebuttal Report, ¶ 69 (“just 9.3% of the total known mutations”); Medin Rebuttal Report, ¶¶ 72–73 (“approximately 9% of all Fabry patients”).

¹¹⁸ Bichet, D.G. *et al.*, (2023) Consensus Recommendations for the Treatment and Management of Patients with Fabry Disease on Migalastat: A Modified Delphi Study, *Front. Med.* **10**:1220637 (ATGAL_08502557 at -558); Chimenti, C. *et al.*, (2020) The GALA Project: Practical Recommendations for the Use of Migalastat in Clinical Practice on the Basis of a Structured Survey Among Italian Experts, *Orphanet J. Rare Dis.* **15**:86 (ATGAL_09796519 at -519).

¹¹⁹ Medin Rebuttal Report, ¶ 67.

time, and/or the impact on quality of life from ERT.¹²⁰ I have discussed this fact extensively in my Opening Report and above citing to multiple scientific articles.¹²¹ As such, it is my opinion that GALAFOLD fulfilled a long-felt but unmet need for those Fabry patients with amenable mutations, including the mutations in the Asserted Claims.

34. Further, as I described above, I do not agree with Dr. Medin that a treatment option needs to be able to treat every single patient to fulfill a long-felt but unmet need.¹²² No medical doctor who treats patients would agree with Dr. Medin. Dr. Medin does not dispute that GALAFOLD is an alternative treatment option for Fabry patients with amenable mutations that are 30–50% of all Fabry patients.¹²³ As such, because certain Fabry patients with amenable mutations prefer GALAFOLD over ERT because as an oral medication it offers improvements to

¹²⁰ See Opening Report, ¶ 61; see, e.g., CADTH Common Drug Review: Clinical Review Report: Migalastat (GALAFOLD) (Feb. 2018) (ATGAL_04833515 at -575); Perretta, F.J., (2023) Fabry Nephropathy: Switch from Enzyme Replacement Therapy to Oral Chaperone Migalastat, *Kidney Int'l Reps.* **8**:S1–S473 at S242–43 (ATGAL_03997641 at -641–42); Aug. 12, 2015 A Trial Patient's Experience with Amicus Therapeutics' Galafold for Fabry Disease (ATGAL_08247330 at -330–31); Apr. 19, 2017 Amicus Briefing Document to FDA (ATGAL_03771237 at -308–30).

¹²¹ Opening Report, ¶¶ 69–72 (citing Moran, N., (2018) FDA Approves Galafold, a Triumph for Amicus, *Nat. Biotech.* **36**:91 (ATGAL_10161450 at -450); Müntze, J. *et al.*, (2023) Patient Reported Quality of Life & Medication Adherence in Fabry Disease Patients Treated with Migalastat: A Prospective, Multicenter Study, *Mol. Genet. Metab.* **138**(2):106981 (ATGAL_03972963); McCafferty, E., Scott, L., (2019) Migalastat: A Review in Fabry Disease, *Drugs* **79**(5):543–54 (ATGAL_10161438 at -446); Wu, Y. *et al.*, (2021) Migalastat Tissue Distribution: Extrapolation from Mice to Humans Using Pharmacokinetic Modeling & Comparison with Agalsidase Beta Tissue Distribution in Mice, *Clinical Pharmacology Drug Dev.* **10**(9):1075–88 (ATGAL_10161482 at -492); Mauer, M. *et al.*, (2017) Reduction of Podocyte Globotriaosylceramide Content in Adult Male Patients with Fabry Disease with Amenable GLA Mutations Following 6 Months of Migalastat Treatment, *J. Med. Genet.* **54**:781 (ATGAL_06818690 at -690)).

¹²² Medin Rebuttal Report, ¶¶ 69, 72–73.

¹²³ Medin Rebuttal Report, ¶ 71.

the time burden associated with treatment and gives more freedom and convenience to patients, it is my opinion that GALAFOLD meets a long-felt but unmet need for such patients over the ERT treatment option.¹²⁴

35. Dr. Medin also opines that “the alleged long-felt unmet need to treat Fabry disease patients according to [me] spans all of the possible mutations migalastat may treat, while overlooking the fact that the claims at issue here are of a significantly narrower scope (i.e., treat significantly fewer mutations and therefore significantly fewer patients).”¹²⁵ He further opines that “[i]t defies logic that claims covering approximately 9% of the known mutations, and approximately 21% of the known amenable mutations, can be commensurate with the scope of the claims.”¹²⁶ I disagree.

36. Dr. Medin ignores the fact that amenable mutations in α -GAL A include the 56 mutations disclosed in the Asserted Claims.¹²⁷ The long-felt but unmet need that was fulfilled by GALAFOLD was for that class of mutations, i.e. amenable mutations. As a medical doctor who has treated Fabry patients for the last 25 years, it is my opinion that for Fabry patients with amenable mutations, there was a long-felt but unmet need for alternative treatments to ERT and GALAFOLD was the treatment option that fulfilled that specific need. My opinion does not change because the Asserted Patents cover a certain subsection of these amenable mutations. Once GALAFOLD was developed and approved, medical doctors started to prescribe it for

¹²⁴ See, e.g., Aug. 12, 2015 A Trial Patient’s Experience with Amicus Therapeutics’ Galafold for Fabry Disease (ATGAL_08247330 at -330–31); Apr. 19, 2017 Amicus Briefing Document to FDA (ATGAL_03771237 at -308–30).

¹²⁵ Medin Rebuttal Report, ¶¶ 67, 69.

¹²⁶ Medin Rebuttal Report, ¶ 70; see Medin Rebuttal Report, ¶¶ 50, 79.

¹²⁷ Opening Report, ¶ 103.

patients with amenable mutations for a variety of reasons which could include that certain patients with such mutations prefer GALAFOLD over the ERT treatment option because of the quality of life, accessibility, intravenous access, or time burdens associated with ERT.¹²⁸

37. Dr. Medin erroneously opines that I only address three specific mutations out of the 56 mutations.¹²⁹ I disagree. In my Opening Report, I have discussed the remaining 53 mutations that were categorized as amenable mutations when GALAFOLD was approved.¹³⁰

3. There Was a Long-Felt But Unmet Need at the Earliest Claimed Priority Date of the Reassessment Mutations Patents and the Engineered Mutations Patent

38. Dr. Medin opines that the references I cited for the technical background section of my Opening Report and one reference that I cite in the long-felt need section of my report post-date the May 30, 2017 priority date of the Reassessment Mutations Patents (but not the August 7, 2019 priority date of the Engineered Mutations Patent).¹³¹ According to Dr. Medin, many of my criticisms of ERT “would be disregarded by a POSA” because the “facts or evidence supporting a long-felt unmet need must predate the filing of the patent application that lead to the issued patent claims in question.”¹³² I’m not a patent lawyer but I do not agree that a person skilled in the art would disregard the scientific literature, particularly here where it confirms that deficiencies in ERT had long been understood. All the criticized references are review articles—

¹²⁸ [REDACTED]

¹²⁹ Medin Rebuttal Report, ¶ 70.

¹³⁰ Opening Report, ¶ 103.

¹³¹ Medin Rebuttal Report, ¶¶ 74–80.

¹³² Medin Rebuttal Report, ¶ 74.

articles that are compilations of work done prior to the articles' publication date—that cite papers that were published before 2017 or are articles that include background information reflecting the state of the art at the time of the relevant priority date and were not themselves used to support that there was a long-felt unmet need.¹³³ As a result, while the review articles may have published after the priority date, their primary sources are from earlier than 2017 and most of these references were cited for background on Fabry disease like its X-linked nature and functions of α -GAL A enzyme in lysosome.¹³⁴ As such, I disagree with Dr. Medin's opinion that

¹³³ See, e.g., Gros, F., Muller, S., (2023) The Role of Lysosomes in Metabolic & Autoimmune Diseases, *Nat. Revs. Nephrology* **19**:366–83 (ATGAL_10161508 at -509–10, -513, -519-21); Sun, A., (2018) Lysosomal Storage Disease Overview, *Ann. Transl. Med.* **6**(24):476 (ATGAL_10161327 at -327); Desnick, R., Ioannou, Y., Eng, C., α -Galactosidase A Deficiency: Fabry Disease, *Online Metabolic & Molecular Bases of Inherited Disease* (McGraw-Hill Education; 2019), pp. 3733–44 (ATGAL_07011379 at -403); Izhar, R. *et al.*, (2023) Fabry Disease in Women: Genetic Basis, Available Biomarkers, & Clinical Manifestations, *Genes* **15**(1):37 (ATGAL_10161341 at -341–42); Arias, E. *et al.*, (2022) Provisional Life Expectancy Estimates for 2021, *Nat'l Ctr. for Health Stat. Reps.* **23** (ATGAL_10161364 at -364); Anania, M. *et al.*, (2025) Identification of Four New Mutations in the GLA Gene Associated with Anderson–Fabry Disease, *Int. J. Mol. Sci.* **26**(2):473 (ATGAL_10161380 at -386); Michaud, M. *et al.*, (2020) When & How to Diagnose Fabry Disease in Clinical Practice, *Am. J. Med. Scis.* **360**(6):641–49 (ATGAL_10161404 at -404); Dutra-Clarke, M. *et al.*, (2021) Variable Clinical Features of Patients with Fabry Disease & Outcome of Enzyme Replacement Therapy, *Mol. Genet. Metab. Reps.* **26**:100700 (ATGAL_10161393 at -393, -395); Lee, H. *et al.*, (2024) 1-Deoxynojirimycin-Producing Bacteria: Production, Optimization, Biosynthesis, Biological Activities, *Biotech. & Bioproc. Eng'g* **29**(6):981–92 (ATGAL_10161496 at -496); McCafferty, E., Scott, L., (2019) Migalastat: A Review in Fabry Disease, *Drugs* **79**(5):543–54 (ATGAL_10161438 at -438); Pieroni, M. *et al.*, (2021) Cardiac Involvement in Fabry Disease, *J. Am. Coll. Cardiology* **77**(7):922–36 (ATGAL_10036328 at -337); Liguori, L. *et al.*, (2020) Pharmacological Chaperones: A Therapeutic Approach for Diseases Caused by Destabilizing Missense Mutations, *Int. J. Mol. Sci.* **21**(2):489 (ATGAL_04808173 at -173).

¹³⁴ E.g., Opening Report, ¶ 44–45; Izhar, R. *et al.*, (2023) Fabry Disease in Women: Genetic Basis, Available Biomarkers, & Clinical Manifestations, *Genes* **15**(1):37 (ATGAL_10161341 at -341–42); Gros, F., Muller, S., (2023) The Role of Lysosomes in Metabolic & Autoimmune Diseases, *Nat. Revs. Nephrology* **19**:366–83 (ATGAL_10161508 at -509–10); Sun, A., (2018) Lysosomal Storage Disease Overview, *Ann. Transl. Med.* **6**(24):476 (ATGAL_10161327 at -327).

the articles I cite would be disregarded by a person of ordinary skill in the art as not describing the state of the art at the relevant time. Further, Dr. Medin criticizes me for citing articles from 2021 and 2024 to support the propositions that in many patients, treatment with ERT causes the patient's immune system to respond by generating anti-drug antibodies and that kidney and heart cells of a Fabry patient take up very limited amounts of recombinant enzyme.¹³⁵ It is undisputed that both of these propositions were well-established before May 30, 2017.¹³⁶

39. Dr. Medin also alleges that the letter submitted to FDA in support of GALAFOLD does not include statements by Fabry patients¹³⁷. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

¹³⁵ Medin Rebuttal Report, ¶ 77.

¹³⁶ See, e.g., Lenders, M. *et al.*, (2016) Serum-Mediated Inhibition of Enzyme Replacement Therapy in Fabry Disease, *J. Am. Soc. Nephrol.* **27**:256–64 (ATGAL_06866922 at -926–28); Thurberg, B. L. *et al.*, (2002) Globotriaosylceramide Accumulation in the Fabry Kidney Is Cleared from Multiple Cell Types After Enzyme Replacement Therapy, *Kidney Int'l* **62**(6):1933–46 (ATGAL_10154771 at -771); Thurberg, B. L. *et al.*, (2009) Cardiac Microvascular Pathology in Fabry Disease: Evaluation of Endomyocardial Biopsies Before and After Enzyme Replacement Therapy, *Circulation* **119**(19):2561–67 (ATGAL_09992372 at -372); see also, e.g., '388 Patent at col.2:22–26; '489 Patent at col.2:37–41; '490 Patent at col.2:37–41.

¹³⁷ Medin Rebuttal Report, ¶ 76.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

a great advantage to receive Migalastat instead of ERT. I feel less like a patient. I

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

It is undeniable that GALAFOLD has fulfilled a long-felt, but unmet need for these Fabry patients who had been treated by ERT previously and for other Fabry patients like them who have amenable mutations in α -GAL A, including patients with the mutations in the Asserted Claims. These patients' experiences are similar to the experiences of my own patients who I treat with migalastat.

40. Dr. Medin opines that I have “zero evidence of a long-felt unmet need.”¹⁴⁵ To support his position, Dr. Medin again points to the fact that ERT is a first-line therapy for treating Fabry patients.¹⁴⁶ As I have discussed in my Opening Report and above in Section V.A.1, ERT being a first-line therapy for Fabry patients does not mean that there was no long-felt but unmet

[REDACTED]

[REDACTED]

¹⁴⁵ Medin Rebuttal Report, ¶ 78.

¹⁴⁶ Medin Rebuttal Report, ¶ 78.

need for Fabry patients with amenable mutations.¹⁴⁷ In my experience, most medical doctors would not agree with Dr. Medin's restrictive view.

41. Further, Dr. Medin criticizes me for not providing information specific to the method of treating Fabry disease with mutations in the Asserted Claims.¹⁴⁸ Dr. Medin further argues that "none of [my] evidence points out the mutations in the asserted claims have been relevant to any Fabry patient."¹⁴⁹ I disagree. As I have repeatedly described in my Opening Report and here, GALAFOLD is a treatment option for all Fabry patients with amenable mutations, and the mutations in the Asserted Claims are among those amenable mutations.¹⁵⁰

[REDACTED]

[REDACTED]

¹⁵¹ As such, I disagree with Dr. Medin's restrictive opinion that, for a rare disease like Fabry where it is not feasible to find publications specific to single mutations due to the overall small sample size of the patients and even smaller size of patients with a specific mutation, a person skilled in the art would not understand that a long-felt but unmet need of Fabry patients with amenable mutations to be applicable to Fabry patients with mutations in the Asserted Claims. As such, I disagree with Dr. Medin's opinion that there is no connection between the Asserted Claims and long-felt

¹⁴⁷ Opening Report, § XI.A.

¹⁴⁸ Medin Rebuttal Report, ¶ 79.

¹⁴⁹ Medin Rebuttal Report, ¶ 79.

¹⁵⁰ Opening Report, ¶¶ 53–54.

¹⁵¹ [REDACTED]

[REDACTED]

unmet need for an alternative treatment option for Fabry patients with amenable mutations, which was met by GALAFOLD.¹⁵²

42. Dr. Medin opines that the August 2018 GALAFOLD label does not include the mutations in the Asserted Claims of the '490 and '164 Patents and therefore there is no nexus for the long-felt need (or failure of others).¹⁵³ The only Asserted Claim of the '490 Patent is Claim 9, which includes a single mutation, I242F.¹⁵⁴ The I242F mutation appears in the GALAFOLD label from August 2018 as an amenable mutation.¹⁵⁵ In fact, Dr. Medin himself agrees that the I242F mutation appears in that label because the same mutation is also included in the Asserted Claims of the '388 Patent and Dr. Medin does not state that in the context of the '388 Patent, the I242F mutation is not included in the label. I disagree with Dr. Medin's opinion that there is no connection between long-felt unmet need and the invention claimed in Claim 9 of the '490 Patent. With respect to the Asserted Claims of the Engineered Mutations Patent (the '164 Patent), I explained in my Opening Report why there was a long-felt unmet need for the inventions claimed in the Asserted Claims of the Engineered Mutations Patent as of August 7, 2019.¹⁵⁶ Dr. Medin appears to analyze those claims as of the wrong date.¹⁵⁷ Elsewhere in his

¹⁵² Medin Rebuttal Report, ¶ 80.

¹⁵³ Medin Rebuttal Report, ¶¶ 81–84; *see* Medin Rebuttal Report, ¶ 48.

¹⁵⁴ '490 Patent, Claim 9.

¹⁵⁵ Aug. 2018 GALAFOLD Prescribing Information (MIGA0107626 at -639).

¹⁵⁶ Opening Report, ¶¶ 73–74.

¹⁵⁷ Medin Rebuttal Report, ¶¶ 81–84.

report, Dr. Medin does not dispute that the priority date of the Engineered Mutations Patent (the '164 Patent) is August 7, 2019.¹⁵⁸

43. Further, I disagree with Dr. Medin that there could not be a long-felt but unmet need for the three mutations in the Asserted Claims of the Engineered Mutations Patent because the mutations were unknown and it was unknown whether they would be associated with Fabry or they would be amenable.¹⁵⁹ Further, he opines that my opinion focuses on early treatment options.¹⁶⁰ As I described in my Opening Report, it is crucial to identify Fabry patients as early as possible and begin their treatment.¹⁶¹ The Engineered Mutations Patent provides a method of treating Fabry patients with previously unknown amenable mutations after such patients are identified and diagnosed. Any time spent in determining whether a previously unknown mutation would be amenable could result in such patient's Fabry disease progression to irreversible organ damage due to delay in starting treatment.

44. Dr. Medin also opines that I provide no evidence that ERT would also not be effective for so-called unknown mutations as an early treatment option or that it was (and is) not used.¹⁶² In my experience, a medical doctor who routinely treats Fabry patients should prescribe the most effective treatment option for a patient. For many Fabry patients with an amenable

¹⁵⁸ Opening Report, ¶ 35; Medin Rebuttal Report, ¶ 82.

¹⁵⁹ Medin Rebuttal Report, ¶ 48.

¹⁶⁰ Medin Rebuttal Report, ¶ 53.

¹⁶¹ Opening Report, ¶¶ 14, 48–49, 74.

¹⁶² Medin Rebuttal Report, ¶ 52.

mutation, that option is GALAFOLD for the reasons I describe in my Opening Report and elsewhere in this report.¹⁶³

45. Dr. Medin also opines that I make assertions regarding drawbacks or side effects of ERT treatment for Fabry disease patients, and my statements still support that ERT was an existing and effective treatment for Fabry disease patients.¹⁶⁴ As an initial matter, I note that Dr. Medin does not dispute what I have listed as drawbacks of ERT in my Opening Report.¹⁶⁵ Further, Dr. Medin seems to allege that if a safe and effective treatment exists, there can be no long-felt but unmet need for any other treatment as he has done elsewhere in his report.¹⁶⁶ I disagree with Dr. Medin's restrictive view as any other medical doctor would as I have described elsewhere here. Further, I do not dispute that ERT is an existing treatment for Fabry patients, but as I have discussed in my Opening Report and here above, I only opine that for certain patients with amenable mutations, GALAFOLD is a preferred alternative treatment option to ERT because of the burdens associated with ERT. GALAFOLD fulfills the long-felt, but unmet need for these patients rather than all Fabry patients.¹⁶⁷ I did not and do not consider GALAFOLD as "a cure-all for any Fabry disease patient or that migalastat can treat any Fabry disease patient."¹⁶⁸ I also disagree with Dr. Medin's opinion that "for a majority of Fabry disease patients, migalastat

¹⁶³ Opening Report, ¶¶ 65–74.

¹⁶⁴ Medin Rebuttal Report, ¶¶ 85–86.

¹⁶⁵ Opening Report, ¶¶ 56–74.

¹⁶⁶ Medin Rebuttal Report, ¶¶ 86, 87.

¹⁶⁷ Opening Report, ¶¶ 65–74.

¹⁶⁸ Medin Rebuttal Report, ¶ 86.

is meaningless.”¹⁶⁹ As a medical doctor who treats Fabry patients regularly, I or any other medical doctor would not consider a treatment option that is available for 30-50% of Fabry patients to be “meaningless.”¹⁷⁰

46. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] A person

skilled in the art would know that GALAFOLD is an alternative treatment option for Fabry patients with amenable mutations and the long-felt but unmet need discussed in the letter (e.g., that additional, non-ERT treatment options were needed) was the need for those patients.

Further, as I described elsewhere in this report, for a rare disease like Fabry where there are limited patients, but many identified disease-causing mutations, a person skilled in the art would not expect a discrete number of mutations to be specifically called out because all Fabry patients with amenable mutations had this long-felt but unmet need for alternative treatment options.

B. Failure of Others

47. In my Opening Report, I opined that the objective indicia of non-obviousness of the Asserted Claims of the Reassessment Mutations Patents is supported by the fact that others

¹⁶⁹ Medin Rebuttal Report, ¶ 86.

¹⁷⁰ Medin Rebuttal Report, ¶ 86; *see* Medin Rebuttal Report, ¶ 71.

¹⁷¹ Medin Rebuttal Report, ¶ 87.

¹⁷² [REDACTED]

tried and failed to find a method of effectively treating Fabry patients with certain α -GAL A mutations with migalastat.¹⁷³ As examples of such failures, I discussed Amicus's collaborations with Shire and GSK; in these collaborations, Amicus and Shire and Amicus and GSK attempted to develop a treatment for Fabry disease using migalastat, but failed to do so.¹⁷⁴ As I discussed in my Opening Report, both Shire and GSK terminated their respective collaborations with Amicus.¹⁷⁵ After these collaborations ended, Amicus spent several more years working to develop migalastat as an alternative treatment option for certain Fabry patients.¹⁷⁶ Amicus's efforts resulted in the approval of GALAFOLD in 2018, fifteen years after the approval of FABRAZYME.¹⁷⁷ In my Opening Report, I pointed to this fifteen-year lag between the approvals of FABRAZYME and GALAFOLD as further evidence of the failure of others to develop a non-ERT treatment for Fabry disease.¹⁷⁸

48. In his rebuttal report, Dr. Medin opines that there is no evidence for failure of others for two main reasons: (1) he opines there is no connection between the failures and the claimed inventions in the Asserted Claims of the Reassessment Mutations Patents, including because ERT already existed to treat Fabry disease; and (2) he opines the failures I reference in

¹⁷³ Opening Report, ¶ 6.

¹⁷⁴ Opening Report, ¶ 75.

¹⁷⁵ Opening Report, ¶¶ 82, 88.

¹⁷⁶ See Opening Report, ¶ 82 (“on October 29, 2009, Shire-Amicus terminated their collaboration”); Opening Report, ¶ 88 (“in November 2013, GSK dropped out of the development collaboration”); Opening Report, ¶ 91 (“on August 10, 2018, FDA approved Amicus's GALAFOLD (migalastat)”).

¹⁷⁷ Opening Report, ¶ 91.

¹⁷⁸ Opening Report, ¶ 91.

my Opening Report are not failures of others, but of Amicus itself.¹⁷⁹ As set forth below, I disagree with each of these opinions.

49. As a preliminary matter, I have not rendered an opinion as to failure of others for the Asserted Claims of the Engineered Mutations Patent. Dr. Medin discusses the '164 Patent (i.e., the Engineered Mutations Patent) in his discussion of the failure of others.¹⁸⁰ In this report, I will only respond to Dr. Medin's opinions related to the Asserted Claims of the Reassessment Mutations Patents.

50. Dr. Medin opines that I failed to connect the failure of others¹⁸¹ with the subject matter of the claims.¹⁸² He further opines that I “conflate[] the general acceptance of migalastat/Galafold® to treat a minority of Fabry disease patients that had amenable mutations” with a general method of treating Fabry (e.g., ERT, a treatment option for any Fabry disease patient before May 2017).¹⁸³ Dr. Medin interprets this to mean that there exists “no nexus” between this objective indicia of non-obviousness and the claimed subject matter.¹⁸⁴ Dr. Medin further opines that “a [person of ordinary skill in the art] would have known that ERT, FDA

¹⁷⁹ Medin Rebuttal Report, ¶¶ 54–62, 85–94.

¹⁸⁰ See Medin Rebuttal Report, ¶¶ 48, 55, 89, 95.

¹⁸¹ I note that Dr. Medin writes that I have “largely failed to connect the so-called industry praise to the claimed subject matter.” Medin Rebuttal Report, ¶ 88. I assume that Dr. Medin meant to write “the failure of others” rather than “the so-called industry praise” in this paragraph because it is included in the section specific to failure of others.

¹⁸² Medin Rebuttal Report, ¶ 88.

¹⁸³ Medin Rebuttal Report, ¶ 88.

¹⁸⁴ Medin Rebuttal Report, ¶ 88.

approved since 2003, effectively treats essentially any Fabry patient regardless of mutation.”¹⁸⁵

As I discuss in Section V.A, I do not dispute that ERT was approved in 2003 and is considered as the standard of care for treating most Fabry patients or that ERT can be effective in treating Fabry disease for certain patients.¹⁸⁶ But ERT does not work for everyone. Also, certain Fabry patients are unwilling to be treated by ERT due to various reasons including the burden on their life-styles.¹⁸⁷ For example, some patients may have difficulty attending frequent infusion treatments that are required by ERT and may end up missing treatments because of the significant burden that infusion appointments place on a patient’s time. For these patients, an oral treatment option like taking a capsule every other day is a better treatment option, which will result in higher patient compliance with the treatment regimen and therefore better outcomes. Other Fabry patients are unable to tolerate ERT and others do not respond or stop responding to ERT. As documented in scientific literature, for certain patients ERT therapy is associated with adverse events like infusion-associated reactions or with antibody formation against ERT that can in turn affect the efficacy of ERT and worsen any infusion-associated reactions.¹⁸⁸ Further, certain patients cannot be treated due to needle phobia, which is common

¹⁸⁵ Medin Rebuttal Report, ¶ 91.

¹⁸⁶ Medin Rebuttal Report, ¶¶ 56, 61, 62, 89.

¹⁸⁷ Opening Report, ¶ 58.

¹⁸⁸ Berry, L. *et al.*, (2024) Patient-Reported Experience with Fabry Disease & Its Management in the Real-World Setting: Results from a Double-Blind, Cross-Sectional Survey of 280 Respondents, *Orphanet J. Rare Dis.* **19**:153 (ATGAL_10161416 at -417); and Bashorum, L. *et al.*, (2022) Burden Associated with Fabry Disease and Its Treatment in 12-15 Year Olds: Results from a European Survey, *Orphanet J. Rare Dis.* **17**:266 (ATGAL_06691824 at -825-26).

in adolescents.¹⁸⁹ Further, for any patient, getting an intravenous infusion every other week is unpleasant and can be painful, especially for a repeated treatment where the patient's veins have been used repeatedly for prior infusions. In addition, in a recent survey of European healthcare workers, all who prescribed or administered ERT to adolescent Fabry patients—before GALAFOLD was approved for adolescent patients in Europe—stated that there was a need for “more manageable treatment options.”¹⁹⁰ In my experience, about one in five ERT patients develop a side effect where ERT cannot be administered to them or have progression of the disease with ERT so their condition will thereafter continue to decline unless they have an alternative treatment option.

51. Alternative treatment options are important to treat any disease, especially because certain treatments may be better for certain patients than others. Any clinician would understand that having one treatment option for a medical condition is not sufficient to meet the needs of every patient. In every disease, treatment options are important, and no clinician would opine otherwise. It is not credible that any medical provider would agree that the existence of ERT eliminates the need for any other treatment options for Fabry disease patients. I therefore disagree with Dr. Medin's insinuation that because ERT existed, no other treatment options were needed for Fabry disease patients,¹⁹¹ and I disagree that the existence of ERT means that there is

¹⁸⁹ Bashorum, L. *et al.*, (2022) Burden Associated with Fabry Disease and Its Treatment in 12-15 Year Olds: Results from a European Survey, *Orphanet J. Rare Dis.* **17**:266 (ATGAL_06691824 at -826)

¹⁹⁰ Bashorum, L. *et al.*, (2022) Burden Associated with Fabry Disease and Its Treatment in 12-15 Year Olds: Results from a European Survey, *Orphanet J. Rare Dis.* **17**:266 (ATGAL_06691824 at -824, -831).

¹⁹¹ Medin Rebuttal Report, ¶ 91.

no connection between the failure of others to develop migalastat as a treatment option and the inventions of the Asserted Claims of the Reassessment Mutations Patents.

52. As stated in my Opening Report, it is my opinion that others have tried and failed to develop the claimed inventions of the Asserted Claims of the Reassessment Mutations Patents, namely, failure to find methods to treat Fabry disease patients with amenable α -GAL A mutations with migalastat.¹⁹² The Asserted Claims of the Reassessment Mutations Patents are directed to treatment of certain Fabry patients with migalastat; they are not directed to a treatment of all Fabry patients in general.¹⁹³ Dr. Medin ignores that the methods of the Asserted Claims of the Reassessment Mutations Patents require “administering migalastat,” rather than treating all Fabry patients with any method.¹⁹⁴ Administering ERT is not a method of treating Fabry disease by administering migalastat.¹⁹⁵ Dr. Medin seems to misunderstand my opinion on the failures of others to develop migalastat as an alternative treatment option to ERT for certain Fabry patients.¹⁹⁶ It is not my opinion that “others had failed to develop a method of treating Fabry disease” or “others had failed to discover the new mutations that are claimed in the [A]sserted [C]laims [of the Reassessment Patents].”¹⁹⁷ As such, I disagree with Dr. Medin’s opinion that

¹⁹² Opening Report, ¶ 75.

¹⁹³ ’388 Patent, Claims 8 and 36; ’489 Patent, Claims 17 and 23, ’490 Patent, Claim 9.

¹⁹⁴ ’388 Patent, Claims 8 and 36; ’489 Patent, Claims 17 and 23, ’490 Patent, Claim 9; Medin Rebuttal Report, ¶¶ 89–90, 93.

¹⁹⁵ Opening Report, ¶¶ 56–59, 62–64.

¹⁹⁶ *E.g.*, Medin Rebuttal Report, ¶¶ 56, 61, 89, 90, 93.

¹⁹⁷ Medin Rebuttal Report, ¶¶ 89, 90; *see* Medin Rebuttal Report, ¶ 93 (“Focusing on the mutations claimed in the claims asserted in this lawsuit, Dr. Jefferies has provided no evidence that any others had tried to find the mutations claimed in the asserted patents but failed.”); Medin Rebuttal Report, ¶¶ 56, 61.

“[my] argument is circular: the claimed mutations were (purportedly) new and known (and whether they were amenable) yet others failed to develop a method to treat them.”¹⁹⁸

53. Dr. Medin opines that Fabry patients with two of the mutations in the Asserted Claims of the Reassessment Mutations Patents (A13P in Claim 8 of the '388 Patent and N34T in Claim 17 of the '489 Patent) had been treated with ERT “successfully,” prior to May 30, 2017.¹⁹⁹ Dr. Medin opines that “[t]hese facts further undermine the idea that others had tried and failed to treat these mutations.”²⁰⁰ First, ERT and migalastat are different treatments for Fabry and the Asserted Claims of the Reassessment Mutations Patents are directed to methods of treating Fabry with migalastat, not with ERT. Second, it is not clear that at least the Fabry patient with A13P mutation was treated successfully.²⁰¹ The reference document does not state which patients were treated successfully.²⁰² However, I note that the reference states that the patients who started on the ERT therapy at an early age showed a better biochemical response than the ones who started at a later age and that the patient with A13P mutation started on the ERT therapy at a later age.²⁰³ Third, a better biochemical response at one given point does not correlate with being treated

¹⁹⁸ Medin Rebuttal Report, ¶ 90.

¹⁹⁹ Medin Rebuttal Report, ¶ 94.

²⁰⁰ Medin Rebuttal Report, ¶ 94.

²⁰¹ Arends, M., (2017) Enzyme Replacement Therapy in Fabry Disease, Towards Individualized Treatment, Universiteit van Amsterdam, UvA-DARE (Digital Academic Repository) (AURO_MEDIN_000341).

²⁰² Arends, M., (2017) Enzyme Replacement Therapy in Fabry Disease, Towards Individualized Treatment, Universiteit van Amsterdam, UvA-DARE (Digital Academic Repository) (AURO_MEDIN_000341).

²⁰³ citing Arends, M., (2017) Enzyme Replacement Therapy in Fabry Disease, Towards Individualized Treatment, Universiteit van Amsterdam, UvA-DARE (Digital Academic Repository) (AURO_MEDIN_000341 at -350, -356).

successfully. In fact, the reference document states that this study “evaluates the biochemical and not the clinical response.”²⁰⁴ Fourth, the study described in the reference document is a retrospective study on Fabry male patients since 1999, before migalastat was approved.²⁰⁵ Lastly, just because a Fabry patient with a certain α -GAL A mutation may have been treated with ERT does not undermine my opinion that others have tried and failed to develop an alternative treatment option for a Fabry patient with the A13P mutation before the approval of GALAFOLD.

54. Dr. Medin similarly opines that “N34T mutation identified in a patient in Australia and treated directly with ERT.”²⁰⁶ Again, Dr. Medin seems to ignore that ERT was the only option for this patient at the time he was treated in 2013 because migalastat was not developed and approved for treatment of certain Fabry patients with certain α -GAL A mutations.²⁰⁷ As the reference article states, at the time, it was not even known that N34T mutation caused Fabry disease, let alone that it is an amenable mutation.²⁰⁸ Because a single Fabry patient with N34T was treated with ERT does not undermine my opinion that others have

²⁰⁴Arends, M., (2017) Enzyme Replacement Therapy in Fabry Disease, Towards Individualized Treatment, Universiteit van Amsterdam, UvA-DARE (Digital Academic Repository) (AURO_MEDIN_000341 at -350).

²⁰⁵Arends, M., (2017) Enzyme Replacement Therapy in Fabry Disease, Towards Individualized Treatment, Universiteit van Amsterdam, UvA-DARE (Digital Academic Repository) (AURO_MEDIN_000341 at -346).

²⁰⁶ Medin Rebuttal Report, ¶ 94 (citing Jamboti J, Forrest C.H., (2017) Fabry Disease; Early Diagnosis Improves Prognosis but Diagnosis Is Often Delayed, *J. Nephropathol.* 6(3):130–33 at 133 (AURO_MEDIN_000361)).

²⁰⁷Jamboti J, Forrest C.H., (2017) Fabry Disease; Early Diagnosis Improves Prognosis but Diagnosis Is Often Delayed, *J. Nephropathol.* 6(3):130–33 at 131-32 (AURO_MEDIN_000361 at -362, -363).

²⁰⁸Jamboti J, Forrest C.H., (2017) Fabry Disease; Early Diagnosis Improves Prognosis but Diagnosis Is Often Delayed, *J. Nephropathol.* 6(3):130–33 at 131 (AURO_MEDIN_000361 at 362).

tried and failed to develop an alternative treatment option for a Fabry patient with the N34T mutation before the approval of GALAFOLD.

55. As discussed in my Opening Report, the purpose of the collaborations between Shire and Amicus and between GSK and Amicus was to develop treatment options for Fabry patients who would respond to treatment with migalastat.²⁰⁹ It is undisputed that each of Shire and GSK exited from their respective collaborations to develop migalastat as an alternative treatment option to ERT for patients with responsive mutations.²¹⁰ As such, it is my opinion that both Shire and GSK failed to develop migalastat as a treatment for Fabry patients with the mutations in the Asserted Claims of the Reassessment Mutations Patents. The Asserted Claims in the Reassessment Mutations Patents relate to methods of treatment of migalastat, with each Asserted Claim directed to a subset of the Fabry patients who respond to migalastat.²¹¹ Thus, each of the claims relates to a subset of the population of patients that Shire and Amicus and GSK and Amicus set out to treat in their respective collaborations. Further, Lukas *et al.* also tried to identify Fabry patients with amenable mutations and failed. Like Shire, GSK and Amicus, this group misidentified certain GLA mutations as potentially non-responsive to migalastat.²¹² Subsequently, Amicus's underlying work leading to the Reassessment Mutations Patents demonstrated that some of these mutations were misidentified as non-responsive to

²⁰⁹ Opening Report, ¶¶ 75, 79, 82–89.

²¹⁰ Opening Report, ¶¶ 75, 79, 82–89.

²¹¹ '388 Patent, Claims 8 and 36; '489 Patent, Claims 17 and 23; '490 Patent, Claim 9.

²¹² Jan Lukas et al., *Functional and Clinical Consequences of Novel α -Galactosidase A Mutations in Fabry Disease*, Human Mutation, Vol. 00, No. 0, 1–9 (2015) (ATGAL_00730664 at -665–666); Jan Lukas et al., *Functional Characterisation of Alpha-Galactosidase A Mutations as a Basis for a New Classification System in Fabry Disease*, PLOS Genetics, Vol 9, Issue 8 (Aug. 2013) (Aug. 2013) (ATGAL_09916904 at -910; ATGAL_01136145).

migalastat but were in fact amenable to migalastat. There is, therefore, a connection between the failures and the Asserted Claims of the Reassessment Mutations Patents. The fact that not every amenable mutation appears in the Asserted Claims of the Reassessment Mutations Patents does not diminish the fact that GSK and Shire collaborations failed to result in the treatment of Fabry patients who would respond to treatment with migalastat, which includes the patients with the mutations in the Asserted Claims of the Reassessment Mutations Patents. I therefore disagree with Dr. Medin's opinion that I "conflate the general acceptance of migalastat to treat certain Fabry disease patients, including the 256 approved HEK assay amenable mutations, with those mutations in the asserted claims in this case."²¹³

56. In my Opening Report, I discussed the connection between the failure of the 011 Study to meet its 6-month endpoints and the Asserted Claims of the Reassessment Mutations Patents.²¹⁴ For example, I explained that the purpose of the 011 Phase 3 study was to compare the effects of migalastat versus a placebo for treatment of patients with Fabry disease and the enrollment criteria included whether the Fabry patient had a GLA mutation that seemed responsive to migalastat based on an experimental in vitro assay.²¹⁵ When the 011 study data was unblinded, it was revealed that the study failed to meet its endpoints., i.e., there was not a significant difference between the group receiving GALAFOLD and the group receiving placebo.²¹⁶ These facts are undisputed by Dr. Medin. Further, Dr. Medin also does not dispute

²¹³ Medin Rebuttal Report, ¶ 93; *see* Medin Rebuttal Report, ¶ 88 ("[Dr. Jefferies] conflates the general acceptance of migalastat/Galafold® to treat a minority of Fabry disease patients that had amenable mutations, with a method of treating Fabry disease writ large.").

²¹⁴ Opening Report, ¶¶ 81, 85.

²¹⁵ Opening Report, ¶ 81.

²¹⁶ Opening Report, ¶ 85.

that the 011 Study was a failure to develop a treatment for Fabry with migalastat for Fabry patients with amenable mutations.²¹⁷ Thus, the failures I discuss in my Opening Report related to the 011 study are failures to treat Fabry patients with GLA mutations that respond to migalastat, and thus are connected to the Asserted Claims of the Reassessment Mutations Patents.²¹⁸ I therefore disagree with Dr. Medin's opinion that I am silent about what the Phase 3 trial's failure to meet its six-month endpoints has to do with the mutations in the asserted claims in this case.²¹⁹

57. In my Opening Report, I also explained that Shire and GSK both decided to terminate their respective collaborations after failing to develop an alternative method of treatment to ERT.²²⁰ Although Dr. Medin opines that Amicus eventually succeeded in developing a method of treating Fabry disease because it received FDA approval for GALAFOLD, Dr. Medin ignores the decade-long history prior to the approval of GALAFOLD, in which the collaboration between Shire and Amicus and the collaboration between GSK and Amicus did end in failures.²²¹ I therefore disagree with Dr. Medin that there is no failure of others because Amicus, alone, continued to innovate and eventually did succeed.²²² Dr. Medin simply ignores the fact that GSK and Shire both failed to develop a treatment for Fabry with

²¹⁷ See Medin Rebuttal Report, ¶ 93 ("the trials were apparently unsuccessful for failure to meet endpoints").

²¹⁸ Opening Report, ¶¶ 75–90.

²¹⁹ Medin Rebuttal Report, ¶ 93.

²²⁰ Opening Report, ¶¶ 75–90.

²²¹ Medin Rebuttal Report, ¶ 92.

²²² Medin Rebuttal Report, ¶¶ 56, 92.

migalastat.²²³ That Amicus later succeeded after years of additional efforts does not negate these prior failures of others—i.e., GSK and Shire. I therefore disagree with his opinion that I presented no evidence of other companies who tried and failed to develop migalastat as a treatment for Fabry disease.²²⁴ Dr. Medin does not provide any support for his speculations about other reasons that GSK may have ended the collaboration.²²⁵ Even if these other reasons were valid, it does not change the fact that GSK tried but did not develop a method of treating Fabry disease with migalastat for the mutations in the Asserted Claims of the Reassessment Mutations Patents. Further, Dr. Medin oversimplifies the interactions with FDA regarding the Phase 3 studies.²²⁶ [REDACTED]

[REDACTED]

[REDACTED]

I also disagree with Dr. Medin’s suggestion that multiple failures of different compounds caused Shire to end the collaboration somehow diminishes the fact that Shire failed to develop

²²³ Opening Report, ¶¶ 75–90.

²²⁴ Medin Rebuttal Report, ¶¶ 56, 92.

²²⁵ Medin Rebuttal Report, ¶ 60.

²²⁶ See Medin Rebuttal Report, ¶ 60 (“Phase III study (011) migalastat failed to meet an endpoint and FDA instructed Amicus to await results from the other Phase III study (012)”).

²²⁷ [REDACTED]

migalastat as a treatment for Fabry disease.²²⁸ Shire still failed to develop a method of treatment for Fabry disease using migalastat regardless of whether it also had an additional failure with respect to another compound. To date, Amicus is the only company to gain FDA approval of a non-ERT treatment for Fabry disease.

58. In my Opening Report, I explained that the fifteen-year lag between the approvals of FABRAZYME and GALAFOLD is further evidence of the failure of others to develop a non-ERT treatment for Fabry disease.²²⁹ Dr. Medin speculates that this lag could have been because there is less incentive to develop products for a rare disease because it will be a small market and there was already an effective therapy.²³⁰ I disagree. As explained in my report, others were interested in developing alternative treatments to ERT, including both Shire and GSK.²³¹ Amicus and others also continued to research and develop such therapies over the course of over a decade.²³² This interest, yet failure to reach FDA approval, suggests that the lag between the approvals of FABRAZYME and GALAFOLD was not due to lack of interest. Further, Dr. Medin

²²⁸ Medin Rebuttal Report, ¶ 59.

²²⁹ Opening Report, ¶ 91.

²³⁰ Medin Rebuttal Report, ¶ 61.

²³¹ Opening Report, ¶¶ 75–90.

²³² See, e.g., Young-Gqamana, B. *et al.*, (2013) Migalastat HCl Reduces Globotriaosylsphingosine (Lyso-Gb3) in Fabry Transgenic Mice and in the Plasma of Fabry Patients, *PLoS One* **8**(3):e57631 (ATGAL_00988929 at -929); Fan, J. Q., Ishii, S., (2010) Pharmacological Chaperone Therapy for Fabry Disease, *Fabry Disease*, 455–68 (ATGAL_01551828–841 at -828); Benjamin, E. R. *et al.*, (2009) The Pharmacological Chaperone 1-Deoxygalactonojirimycin Increases α -Galactosidase A Levels in Fabry Patient Cell Lines, *J. of Inherited Metabolic Disease* **32**(3):424–440 (ATGAL_10161677 at-677).

himself researches other therapies to treat Fabry disease, which further undermines his opinion that there is a lack of interest in developing such therapies.²³³

C. Industry Praise

59. In my Opening Report, I identified several sources of praise for the inventions in the Asserted Claims of the Reassessment Mutations Patents, including (1) the 2019 National Organization for Rare Disorders (“NORD”) Industry Innovation Award; (2) the 2018 UK Prix Galien Medal for Innovative Product; and (3) healthcare provider opinions praising GALAFOLD.²³⁴

60. In his rebuttal report, Dr. Medin criticizes my opinions on industry praise for the inventions in the Asserted Claims of the Reassessment Mutations Patents.²³⁵ As explained further below, I disagree with Dr. Medin’s criticisms.

1. Connection Between the Industry Praise and the Claimed Inventions

61. I refer to FDA’s approval of GALAFOLD and GALAFOLD’s label to explain why there is a connection between the industry praise that I reference and the Asserted Claims in the Reassessment Mutations Patents.²³⁶ Each of the mutations in the Asserted Claims of the Reassessment Mutations Patents were included in the original GALAFOLD label when it was

²³³ Khan, A. *et al.*, (2024) Lentivirus-Mediated Gene Therapy for Fabry Disease: 5-Year End-of-Study Results from the Canadian FACTs Trial, *Clin. Transl. Med.* **15**(1) (AURO_MEDIN_000025 at -025); Khan, A. *et al.*, (2021) Lentivirus-Mediated Gene Therapy for Fabry Disease, *Nat. Comm’s* **12**:1178 (ATGAL_10036350 at -350).

²³⁴ Opening Report, ¶¶ 92–103.

²³⁵ Medin Rebuttal Report, ¶¶ 96–101.

²³⁶ Opening Report, ¶¶ 96–97, 99, 102–103.

FDA approved in August 2018.²³⁷ Industry praise for GALAFOLD therefore includes praise for the ability to treat the Fabry patients with the mutations in the Asserted Claims of the Reassessment Mutations Patents. Dr. Medin therefore misunderstands my references to the FDA approval and GALAFOLD's label with respect to the industry praise I reference in my report.²³⁸ I do not cite the FDA approval or GALAFOLD label themselves as industry praise, but rather to show the connection between the Asserted Claims of the Reassessment Mutations Patents and the industry praise that I do reference. I therefore disagree with Dr. Medin's opinion that I failed to connect the industry praise that I identified in my report to the claimed subject matter.²³⁹

62. Further, while it is true that not every amenable mutation appears in the Asserted Claims of the Reassessment Mutations patents, the praise for GALAFOLD includes praise for its ability to treat Fabry patients with the mutations in the Asserted Claims of the Reassessment

²³⁷ Opening Report, ¶¶ 96–97, 99, 102–03.

²³⁸ Medin Rebuttal Report, ¶ 97 (“Dr. Jefferies cites the FDA approved product label and for their listing of certain mutations. He conflates this information with praise for the specific mutations in the asserted patents. Nowhere does Dr. Jefferies connect this purported praise with the Galafold® label, or the specific claims at issue here” (citations omitted)).

²³⁹ Medin Rebuttal Report, ¶ 96; *see* Medin Rebuttal Report, ¶ 98 (“The Galafold® label lists 348 mutations. In the sources cited by Dr. Jefferies, the drug migalastat/Galafold® is being discussed generally. None of this so-called praise, however, makes reference to the specific mutations claimed or the amount of migalastat administered. The so-called praise concerns migalastat to treat Fabry disease patients with HEK assay amenable mutations, generally. And while that may be true it is irrelevant to the question of industry praise for the claimed subject matter at issue in this case. Therefore, I disagree with Dr. Jefferies that the materials he relies on show industry praise for the subject matter claimed in the asserted claims in this case.”); Medin Rebuttal Report, ¶ 13 (“[Dr. Jefferies] conflates the general acceptance of migalastat/Galafold® to treat a minority of Fabry disease patients that had amenable mutations, with a method of treating Fabry disease writ large – and also with the specific mutations in the claims asserted in this case.”); Medin Rebuttal Report, ¶ 88.

Mutations Patents. I therefore disagree with Dr. Medin's suggestion that this industry praise is not related to the Asserted Claims of the Reassessment Mutations Patents.²⁴⁰

2. 2019 NORD Industry Innovation Award

63. Dr. Medin does not dispute that the 2019 NORD Industry Innovation Award demonstrates industry praise for methods of treatment using GALAFOLD.²⁴¹

64. Dr. Medin incorrectly states that I have not established nexus between the 2019 NORD Industry Innovation Award and the Asserted Claims in the Reassessment Mutations Patents.²⁴² But I refer to FDA's approval of GALAFOLD and GALAFOLD's label to explain why there is a connection between the NORD Industry Innovation Award and the Asserted Claims in the Reassessment Mutations Patents.²⁴³ For example, as I explained in my Opening Report, each of the mutations in the Asserted Claims of the Reassessment Mutations Patents were included in the original GALAFOLD label when it was FDA approved in August 2018.²⁴⁴ The NORD Industry Innovation Award for GALAFOLD therefore includes praise for the ability to treat Fabry patients with the mutations in the Asserted Claims of the Reassessment Mutations Patents.

²⁴⁰ Medin Rebuttal Report, ¶ 96.

²⁴¹ See Medin Rebuttal Report, ¶¶ 96–101.

²⁴² Medin Rebuttal Report, ¶¶ 96–97.

²⁴³ Opening Report, ¶¶ 96–97.

²⁴⁴ Opening Report, ¶¶ 96–97.

65. Dr. Medin misunderstands my reference to GALAFOLD's FDA approval and label with respect to the NORD Industry Innovation Award.²⁴⁵ I do not cite the FDA approval or label as industry praise, but rather to show the connection between the Asserted Claims of the Reassessment Mutations Patents and the industry praise that I do reference.²⁴⁶ I therefore disagree with Dr. Medin's opinion that I "do[] not assert that the NORD [] award[] mentioned any mutations at all, including the ones in the asserted claims" and that my "assertions and analysis insinuate some connection, but [I] state[] none."²⁴⁷

3. 2018 UK Prix Galien Medal for Innovative Product

66. Dr. Medin incorrectly states that I have not established nexus between the 2018 UK Prix Galien Medal for Innovative Product and the Asserted Claims in the Reassessment Mutations Patents.²⁴⁸ I refer to FDA's approval of GALAFOLD and GALAFOLD's label to explain why there is a connection between the 2018 UK Prix Galien Medal for Innovative Product and the Asserted Claims in the Reassessment Mutations Patents.²⁴⁹ For example, as I explained in my Opening Report, many of the mutations in the Asserted Claims of the Reassessment Mutations Patents were included in the original GALAFOLD label when it was

²⁴⁵ Medin Rebuttal Report, ¶ 97 ("Dr. Jefferies cites the FDA approved product label and for their listing of certain mutations. He conflates this information with praise for the specific mutations in the asserted patents. Nowhere does Dr. Jefferies connect this purported praise with the Galafold® label, or the specific claims at issue here." (citations omitted)).

²⁴⁶ Opening Report, ¶¶ 96–97.

²⁴⁷ Medin Rebuttal Report, ¶ 97.

²⁴⁸ Medin Rebuttal Report, ¶¶ 96–97.

²⁴⁹ Opening Report, ¶¶ 98–99.

approved in Europe in 2016.²⁵⁰ Specifically, the original EU label for GALAFOLD includes all of the mutations in Claim 9 of the '490 Patent and Claim 23 of the '489 Patent, along with many of the mutations in Claims 8 and 36 of the '388 Patent and Claim 17 of the '489 Patent.²⁵¹ The 2018 UK Prix Galien Medal for Innovative Product for GALAFOLD therefore includes praise for the ability to treat the Fabry patients with the mutations in the Asserted Claims of the Reassessment Mutations Patents.

67. Dr. Medin misunderstands my reference to GALAFOLD's FDA approval and label with respect to the 2018 UK Prix Galien Medal for Innovative Product.²⁵² I do not cite the FDA approval or GALAFOLD label as industry praise, but rather to show the connection, or nexus, between the Asserted Claims of the Reassessment Mutations Patents and the industry praise that I do reference.²⁵³ I therefore disagree with Dr. Medin's opinion that I "do[] not assert that the [] Prix Galien award[] mentioned any mutations at all, including the ones in the asserted claims" and that my "assertions and analysis insinuate some connection, but [I] state[] none."²⁵⁴

68. Dr. Medin also misunderstands my opinion with respect to the Prix Galien Medal.²⁵⁵ It is not my opinion that the industry-focused Prix Galien Medal is equivalent to a

²⁵⁰ Opening Report, ¶ 99.

²⁵¹ Opening Report, ¶ 99; Commission Implementing Decision, Annex I: Summary of Product Characteristics (ATGAL_03760350 at -059–64).

²⁵² Medin Rebuttal Report, ¶ 97 ("Dr. Jefferies cites the FDA approved product label and for their listing of certain mutations. He conflates this information with praise for the specific mutations in the asserted patents. . . Nowhere does Dr. Jefferies connect this purported praise with the Galafold® label, or the specific claims at issue here." (citations omitted)).

²⁵³ Opening Report, ¶ 99.

²⁵⁴ Medin Rebuttal Report, ¶ 97.

²⁵⁵ Medin Rebuttal Report, ¶¶ 99–101.

Nobel Prize. Nevertheless, the Prix Galien Medal is a prestigious award and, in my opinion, clinicians in the industry, myself included, would be aware of this award and would view winning the award as a prestigious accomplishment and as praise from the industry. I, therefore, disagree with Dr. Medin's criticisms of the Prix Galien organization and the organization's description of its awards and with Dr. Medin's suggestion that the Prix Galien Medal is not prestigious.²⁵⁶

69. Dr. Medin tries to minimize the importance of the Prix Galien Medal by focusing on the number of awards given in different countries.²⁵⁷ However, Dr. Medin does not dispute that Amicus won this award for GALAFOLD, nor does he dispute that this award is indicative of industry praise for GALAFOLD. By focusing on total number of 2018 awards rather than their substance, Dr. Medin ignores that there were three separate award categories—best pharmaceutical product, best biotechnology product, and best medical technology—and only one product won in the best pharmaceutical product category.²⁵⁸ These criticisms do not negate the praise for GALAFOLD or prestige of the award.

4. Healthcare Provider Opinions Praising GALAFOLD

70. Dr. Medin does not dispute that healthcare providers praised GALAFOLD and the benefits it offers to their patients for the reasons cited in my Opening Report.²⁵⁹

²⁵⁶ Medin Rebuttal Report, ¶¶ 99–101.

²⁵⁷ Medin Rebuttal Report, ¶ 99.

²⁵⁸ Medin Rebuttal Report, ¶ 99; The Galien Foundation Announces 2018 #PrixGalien Award Recipients, PR Newswire (Oct. 26, 2018), <https://www.prnewswire.com/news-releases/the-galien-foundation-announces-2018-prixgalien-award-recipients-300738574.html#:~:text=%22The%20Committee%20had%20the%20unique> (AURO_MEDIN_000365 at -365)

²⁵⁹ See Medin Rebuttal Report, ¶¶ 96–101.

71. I refer to FDA’s approval of GALAFOLD and GALAFOLD’s label to explain why there is a connection between the industry praise and the Asserted Claims in the Reassessment Mutations Patents.²⁶⁰ For example, as I explained in my Opening Report, each of the mutations in the Asserted Claims of the Reassessment Mutations Patents were included in the original GALAFOLD label when it was FDA approved in August 2018.²⁶¹ Healthcare prescribers’ praise for GALAFOLD therefore includes praise for the ability to treat the Fabry patients with the mutations in the Asserted Claims of the Reassessment Mutations Patents. Dr. Medin misunderstands my reference to the FDA approval and GALAFOLD’s label with respect to healthcare provider’s praise for GALAFOLD.²⁶² I do not cite the FDA approval or GALAFOLD label as industry praise, but rather to show the connection between the Asserted Claims of the Reassessment Mutations Patents and the industry praise by healthcare providers.²⁶³ Therefore, I disagree with Dr. Medin that there is no connection between the Asserted Claims of the Reassessment Mutations Patents and such praise.²⁶⁴

VI. CONCLUSION

72. For the reasons discussed in this report and in my Opening Report, in my opinion, (1) there was a long-felt but unmet need for Amicus’s inventions in the Asserted Claims;

²⁶⁰ Opening Report, ¶¶ 102–03.

²⁶¹ Opening Report, ¶¶ 102–03.

²⁶² Medin Rebuttal Report, ¶ 97 (“Dr. Jefferies cites the FDA approved product label and for their listing of certain mutations. He conflates this information with praise for the specific mutations in the asserted patents. . . Nowhere does Dr. Jefferies connect this purported praise with the Galafold® label, or the specific claims at issue here.” (citations omitted)).

²⁶³ Opening Report, ¶¶ 102–03.

²⁶⁴ Medin Rebuttal Report, ¶ 98.

(2) there were failures of others to solve the problems solved by Amicus's inventions claimed in the Asserted Claims of the Reassessment Mutations Patents; and (3) there was industry praise for Amicus's inventions claimed in the Asserted Claims of the Reassessment Mutations Patents.

I declare under penalty of perjury that the foregoing is true and correct.

Dated: 5/23/2025

A handwritten signature in blue ink, appearing to read "John L. Jefferies", is positioned above a horizontal line.

John L. Jefferies, M.D.

EXHIBIT 1

Exhibit 1**Additional Materials Considered**

Beginning Bates Number or Bates Range for Excerpt	Document
ATGAL_00047810–907	Oct. 7, 2014, Clinical Study Report AT1001-018
ATGAL_00076781–877	Dec. 5, 2013, Amended Clinical Study Report AT1001-015
ATGAL_00092978–3067	Sept. 8, 2010, Clinical Study Report AT1001-FAB-CL-201
ATGAL_00096062–137	Sept. 13, 2011, Clinical Study Report AT1001-FAB-CL-202
ATGAL_00097754–832	June 20, 2011, Clinical Study Report AT1001-FAB-CL-203
ATGAL_00154581–666	Dec. 19, 2014, Clinical Study Report AT1001-FAB-CL-205
ATGAL_00730664	Jan Lukas et al., <i>Functional and Clinical Consequences of Novel α-Galactosidase A Mutations in Fabry Disease</i> , Human Mutation, Vol. 00, No. 0, 1–9 (2015)
ATGAL_00988929	Young-Gqamana, B. <i>et al.</i> , (2013) Migalastat HCl Reduces Globotriaosylsphingosine (Lyso-Gb3) in Fabry Transgenic Mice and in the Plasma of Fabry Patients, <i>PLoS One</i> 8(3):e57631
ATGAL_01551828–841	Fan, J. Q., Ishii, S., (2010) Pharmacological Chaperone Therapy for Fabry Disease, <i>Fabry Disease</i> , 455–68
ATGAL_03366897–992	Dec. 11, 2012, Clinical Study Report AT1001-014
ATGAL_03760350	Commission Implementing Decision, Annex I: Summary of Product Characteristics
ATGAL_03872004–092	Feb. 15, 2017, Clinical Study Report AT1001-041
ATGAL_03997641	Perretta, F.J., (2023) Fabry Nephropathy: Switch from Enzyme Replacement Therapy to Oral Chaperone Migalastat, <i>Kidney Int'l Reps.</i> 8:S1–S473 at S242–43
ATGAL_04636868	Advice/Information Request from B. Nikhar, MD, Acting Deputy Director, Div. of Gastroenterology and Inborn Errors Prods., Ctr. for Drug Evaluation and Rsch., Food and Drug Admin. to D. Odumosu, MS, Exec. Dir., Glob. Regul. Affairs, Amicus Therapeutics (Jan. 30, 2019)
ATGAL_04833515	CADTH Common Drug Review: Clinical Review Report: Migalastat (GALAFOLD) (Feb. 2018)

Beginning Bates Number or Bates Range for Excerpt	Document
ATGAL_06500087	Germain, D.P. <i>et al.</i> , (2016) Treatment of Fabry's Disease with Pharmacologic Chaperone Migalastat, <i>N. Engl. J. Med.</i> 375(6):545–55
ATGAL_06691824	Bashorum, L. <i>et al.</i> , (2022) Burden Associated with Fabry Disease and Its Treatment in 12-15 Year Olds: Results from a European Survey, <i>Orphanet J. Rare Dis.</i> 17:266
ATGAL_07915907	Schiffmann, R. <i>et al.</i> , (2018), Migalastat Improves Diarrhea in Patients with Fabry Disease: Clinical-Biomarker Correlations from the Phase 3 FACETS Trial, <i>Orphanet J. Rare Dis.</i> 13(1):68
ATGAL_08454411	Alegra, T. <i>et al.</i> , (2012) Enzyme Replacement Therapy for Fabry Disease: A Systematic Review and Meta-Analysis, <i>Genet. Mol. Biol.</i> 35(4 supp.):947–54
ATGAL_08502557	Bichet, D.G. <i>et al.</i> , (2023) Consensus Recommendations for the Treatment and Management of Patients with Fabry Disease on Migalastat: A Modified Delphi Study, <i>Front. Med.</i> 10:1220637
ATGAL_08508336	Riccio, E. <i>et al.</i> , (2020) Switch from Enzyme Replacement Therapy to Oral Chaperone Migalastat for Treating Fabry Disease: Real-Life Data, <i>Eur. J. of Hum. Genetics</i> 28:1662–68
ATGAL_09796519	Chimenti, C. <i>et al.</i> , (2020) The GALA Project: Practical Recommendations for the Use of Migalastat in Clinical Practice on the Basis of a Structured Survey Among Italian Experts, <i>Orphanet J. Rare Dis.</i> 15:86
ATGAL_09818936	Burlina, A., Politei, J., (2016) The Central Nervous System Involvement in Fabry Disease: A Review, <i>J. of Inborn Errors of Metabolism and Screening</i> 4:1–7
ATGAL_09877685	Germain, D. <i>et al.</i> , (2019) Efficacy of the Pharmacologic Chaperone Migalastat in a Subset of Male Patients with the Classic Phenotype of Fabry Disease and Migalastat-Amenable Variants: Data from the Phase 3 Randomized, Multicenter, Double-Blind Clinical Trial and Extension Study, <i>Genet. Med.</i> 21(9):1987–97
ATGAL_09879249	Sims, K. <i>et al.</i> , (2009) Stroke in Fabry Disease Frequently Occurs Before Diagnosis and in the Absence of Other Clinical Events: Natural History Data from the Fabry Registry, <i>Stroke</i> 40(3):788–94

Beginning Bates Number or Bates Range for Excerpt	Document
ATGAL_09916904 ATGAL_01136145	Jan Lukas et al., <i>Functional Characterisation of Alpha-Galactosidase A Mutations as a Basis for a New Classification System in Fabry Disease</i> , PLOS Genetics, Vol 9, Issue 8 (Aug. 2013)
ATGAL_09992372	Thurberg, B. L. <i>et al.</i> , (2009) Cardiac Microvascular Pathology in Fabry Disease: Evaluation of Endomyocardial Biopsies Before and After Enzyme Replacement Therapy, <i>Circulation</i> 119(19):2561–67
ATGAL_10023551	Bichet, D. <i>et al.</i> , (2021) Assessment of Plasma Lyso-Gb3 for Clinical Monitoring of Treatment Response in Migalastat-Treated Patients with Fabry Disease, <i>Genet. Med.</i> 23(1):192–201
ATGAL_10036350	Khan, A. <i>et al.</i> , (2021) Lentivirus-Mediated Gene Therapy for Fabry Disease, <i>Nat. Commc'ns</i> 12:1178
ATGAL_10154771	Thurberg, B. L. <i>et al.</i> , (2002) Globotriaosylceramide Accumulation in the Fabry Kidney Is Cleared from Multiple Cell Types After Enzyme Replacement Therapy, <i>Kidney Int'l</i> 62(6):1933–46
ATGAL_10161674	Amicus Therapeutics Announces Positive Phase 3 Data on Cardiac and Composite Endpoints from Fabry Monotherapy Study 012 at American Society of Nephrology, <i>Pipeline Review</i> (Nov. 17, 2014), https://pipelinereview.com/amicus-therapeutics-announces-positive-phase-3-data-on-cardiac-and-composite-endpoints-from-fabry-monotherapy-study-012-at-american-society-of-nephrology
ATGAL_10161677	Benjamin, E. R. <i>et al.</i> , (2009) The Pharmacological Chaperone 1-Deoxygalactonojirimycin Increases α -Galactosidase A Levels in Fabry Patient Cell Lines, <i>J. of Inherited Metabolic Disease</i> 32(3):424–440
ATGAL_10161694	Blaszczyk, B. <i>et al.</i> , (2023) Fabry Disease and Sleep Disorders: A Systematic Review, <i>Front. Neurol.</i> 14:1217618
ATGAL_10161704	Müller, M., Neuropsychiatric and Psychosocial Aspects of Fabry Disease, <i>Fabry Disease: Perspectives from 5 Years of FOS</i> (NCBI Bookshelf; 2006)
ATGAL_10161722	Gambardella, J. <i>et al.</i> , (2024) Fatigue as Hallmark of Fabry Disease: Role of Bioenergetic Alterations, <i>Front. Cardiovasc. Med.</i> 11:1341590

Beginning Bates Number or Bates Range for Excerpt	Document
ATGAL_10161730	Hendriksz, C.J. <i>et al.</i> , (2018) Risks of Long-Term Port Use in Enzyme Replacement Therapy for Lysosomal Storage Disorders, <i>Mol. Genet. Metab. Reps.</i> 15:71–73
ATGAL_10161733	Humphrey, P.P.A., (2008) The Discovery and Development of the Triptans, a Major Therapeutic Breakthrough, <i>Headache</i> 48:685–87
ATGAL_10161752	A Study of AT1001 (Migalastat Hydrochloride) in Participants with Fabry Disease, ClinicalTrials.gov, https://clinicaltrials.gov/study/NCT00214500
ATGAL_10161764	A 24-Week Safety and Pharmacodynamic Study of AT1001 (Migalastat Hydrochloride) in Participants with Fabry Disease, ClinicalTrials.gov, https://clinicaltrials.gov/study/NCT00283933
ATGAL_10161774	A 12-Week Safety and Pharmacodynamic Study of AT1001 (Migalastat Hydrochloride) in Participants with Fabry Disease, ClinicalTrials.gov, https://clinicaltrials.gov/study/NCT00283959
ATGAL_10161784	Open-Label Long-Term Safety Study of AT1001 (Migalastat Hydrochloride) in Participants with Fabry Disease Who Have Completed a Previous AT1001 Study, ClinicalTrials.gov, https://clinicaltrials.gov/study/NCT00526071
ATGAL_10161794	Study of the Effects of Oral AT1001 (Migalastat Hydrochloride) in Patients with Fabry Disease, ClinicalTrials.gov, https://clinicaltrials.gov/study/NCT00925301
ATGAL_10161809	Study to Evaluate Ecallantide in Paediatric Patients with Acute Attacks of Hereditary Angioedema, ClinicalTrials.gov, https://clinicaltrials.gov/study/NCT01253382
ATGAL_10161817	Safety and Efficacy of QAX576 in Patients with Idiopathic Pulmonary Fibrosis (IPF), ClinicalTrials.gov, https://clinicaltrials.gov/study/NCT01266135
ATGAL_10161827	Open-Label Phase 3 Long-Term Safety Study of Migalastat (AT1001-041), ClinicalTrials.gov, https://clinicaltrials.gov/study/NCT01458119
ATGAL_10161840	Schiffmann, R., Moore, D.F., Neurological Manifestations of Fabry Disease, Fabry Disease: Perspectives from 5 Years of FOS (NCBI Bookshelf; 2006)

Beginning Bates Number or Bates Range for Excerpt	Document
ATGAL_10161856	Nowicki, M. <i>et al.</i> , (2024) A Review and Recommendations for Oral Chaperone Therapy in Adult Patients with Fabry Disease, <i>Orphanet J. Rare Dis.</i> 19:16
ATGAL_10161869	Peters, G. L., (2019) Migraine Overview and Summary of Current and Emerging Treatment Options, <i>Am. J. Manag. Care</i> 25(2 Suppl):S23–S34
ATGAL_10161911	Rees, C. A. <i>et al.</i> , (2019) Noncompletion and Nonpublication of Trials Studying Rare Diseases: A Cross-Sectional Analysis, <i>PLoS Med.</i> 16(11):e1002966
ATGAL_10161927	Elizabeth Pratt, How Migraine Treatments Have Changed Over Time, <i>Med. News Today</i> (Sept. 12, 2024), https://www.medicalnewstoday.com/articles/migraine-treatments-history
MIGA0107626	Aug. 2018 GALAFOLD Prescribing Information

EXHIBIT D

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE**

AMICUS THERAPEUTICS US, LLC
and AMICUS THERAPEUTICS, INC.,

Plaintiffs,

v.

TEVA PHARMACEUTICALS USA, INC.
and TEVA PHARMACEUTICALS, INC., et al.

Defendants.

C.A. No. 1:22-cv-01461-CJB

ANDA CASE

(Consolidated)

OPENING REPORT OF DR. JEFFREY A. MEDIN ON PATENT INVALIDITY

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I. INTRODUCTION

1. I, Jeffrey A. Medin, Ph.D., submit this report pursuant to Fed. R. Civ. P. 26(a)(2)(B) on behalf of Defendant Aurobindo Pharma Ltd. and Aurobindo Pharma USA Inc. (“Defendants” or “Aurobindo”).

2. I have been informed that Plaintiffs, Amicus Therapeutics US, LLC and Amicus Therapeutics, Inc. (“Plaintiffs” or “Amicus”) allege that Aurobindo’s proposed migalastat product infringes certain claims of U.S. Patent Nos. 11,633,388 (“the ’388 patent”), 11,833,164 (“the ’164 patent”), 12,042,489 (“the ’489 patent”), and 12,042,490 (“the ’490 patent”) (collectively, “Patents-in-Suit”). I understand that the asserted claims are:

- Claims 8, 36 of the ’388 patent
- Claims 23-27 of the ’164
- Claims 17 and 19 of the ’489 patent
- Claim 9 of the ’490 patent

3. Additionally, if asked, I may respond to any opinions or testimony of Plaintiff’s expert witnesses regarding issues within my area of expertise. I expect that I may be called to testify at the trial in these proceedings. If called to testify, my testimony may include an explanation of the scientific principles that underlie the opinions expressed in this report. If any further developments occur in this litigation that may bear upon the opinions I have expressed in this report, I reserve the right to supplement or amend this report to take those developments into account. In the event Plaintiffs submit any response to my expert report, I reserve the right to respond to any issues raised by that response.

the named inventor(s); (2) the type of problems encountered in the art; (3) the prior art solutions to those problems; (4) the speed with which innovations are made; and (5) the sophistication of the technology and educational level of active workers in the field.

30. In my opinion, a POSA to whom the '388, '489, '490, and '164 patents are directed, and given the seriousness of the potential health risks associated with administering pharmaceutical agents, suggests that one of ordinary skill in the field of pharmaceutical research and development would have a fairly high level of education and skill. Such skilled artisans would be those familiar with the field of metabolic disorders such as Fabry disease and would include pharmaceutical chemists or physicians involved in research and development of formulations for treatment of such disorders, who would have a Master's, Ph.D., and/or M.D. degree and several years of experience in the field. The amount of experience in the field would depend upon the level of formal education and particular experience with drugs for the treatment of Fabry disease. A POSA would have worked in conjunction with other individuals, the group of which collectively would have had experience in these fields, as well as in the field of clinical development of drugs for the treatment of Fabry disease patients having renal impairment. A POSA would also have knowledge of the scientific literature concerning these fields as of the claimed priority dates of the asserted patents. A POSA may also work as part of a multidisciplinary team and draw upon not only his or her own skills but also take advantage of certain specialized skills of others in the team to solve a given problem. Therefore, in performing the second and third inquiries of an obviousness determination, the prior art must be viewed from the perspective of such an ordinarily skilled person, who would easily have understood the prior art references referred to herein and would have the capacity to draw inferences from them.

XI. COMPENSATION

296. I am being compensated for my time in connection with this proceeding at my standard consulting rate of \$400 per hour for non-testifying time and \$400 per hour for deposition and trial testimony, which is independent of the outcome of this proceeding.

XII. PRIOR TESTIMONY

297. In the past four years, I have not testified as an expert witness at deposition or at trial.

XIII. RESERVATION OF RIGHTS

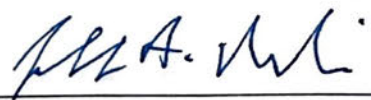
298. I have based my opinions and analysis on documents and information available to me at the time I signed this report. If, and when, any new evidence arises, I reserve the right to supplement or modify my opinions to reflect that evidence.

299. In the event that Plaintiff submits any response to this expert report, I reserve the right to respond to any issues raised by such a response.

300. If called to testify, my testimony may include an explanation of the scientific principles that underlie the opinions expressed in this report.

301. I reserve the right to make and use demonstratives to help explain my opinions.

Dated: April 4, 2025



Jeffrey A. Medin, Ph.D.

EXHIBIT E



US011633388B2

(12) **United States Patent**
Castelli et al.(10) **Patent No.:** **US 11,633,388 B2**(45) **Date of Patent:** **Apr. 25, 2023**(54) **METHODS OF TREATING FABRY PATIENTS HAVING RENAL IMPAIRMENT**(71) Applicant: **Amicus Therapeutics, Inc.**, Cranbury, NJ (US)(72) Inventors: **Jeff Castelli**, New Hope, PA (US);
Elfrida Benjamin, Millstone Township, NJ (US)(73) Assignee: **Amicus Therapeutics, Inc.**, Philadelphia, PA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 299 days.

(21) Appl. No.: **17/078,765**(22) Filed: **Oct. 23, 2020**(65) **Prior Publication Data**

US 2021/0038582 A1 Feb. 11, 2021

Related U.S. Application Data

(60) Continuation of application No. 16/817,881, filed on Mar. 13, 2020, now Pat. No. 10,857,141, which is a continuation of application No. 16/678,183, filed on Nov. 8, 2019, now Pat. No. 10,874,655, which is a division of application No. 16/284,582, filed on Feb. 25, 2019, now Pat. No. 10,471,053, which is a division of application No. 15/992,336, filed on May 30, 2018, now Pat. No. 10,251,873.

(60) Provisional application No. 62/626,953, filed on Feb. 6, 2018, provisional application No. 62/512,458, filed on May 30, 2017.

(51) **Int. Cl.****A61K 31/445** (2006.01)**A61P 13/12** (2006.01)**A61K 9/48** (2006.01)(52) **U.S. Cl.**CPC **A61K 31/445** (2013.01); **A61P 13/12** (2018.01); **A61K 9/48** (2013.01)(58) **Field of Classification Search**CPC **A61K 31/445**USPC **514/315**

See application file for complete search history.

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Primary Examiner — Raymond J Henley, III
(74) *Attorney, Agent, or Firm* — Servilla Whitney LLC(57) **ABSTRACT**Provided are methods for treatment of Fabry disease in patients having HEK assay amenable mutations in α -galactosidase A. Certain methods comprise administering migalastat or a salt thereof every other day, such as administering about 150 mg of migalastat hydrochloride every other day.**51 Claims, 21 Drawing Sheets****Specification includes a Sequence Listing.**

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-continued

Trp	Pro	Phe	Gln	Lys	Pro	Asn	Tyr	Thr	Glu	Ile	Arg	Gln	Tyr	Cys	Asn
210						215					220				
His	Trp	Arg	Asn	Phe	Ala	Asp	Ile	Asp	Asp	Ser	Trp	Lys	Ser	Ile	Lys
225				230						235				240	
Ser	Ile	Leu	Asp	Trp	Thr	Ser	Phe	Asn	Gln	Glu	Arg	Ile	Val	Asp	Val
			245						250				255		
Ala	Gly	Pro	Gly	Gly	Trp	Asn	Asp	Pro	Asp	Met	Leu	Val	Ile	Gly	Asn
			260					265					270		
Phe	Gly	Leu	Ser	Trp	Asn	Gln	Gln	Val	Thr	Gln	Met	Ala	Leu	Trp	Ala
		275				280						285			
Ile	Met	Ala	Ala	Pro	Leu	Phe	Met	Ser	Asn	Asp	Leu	Arg	His	Ile	Ser
	290					295					300				
Pro	Gln	Ala	Lys	Ala	Leu	Leu	Gln	Asp	Lys	Asp	Val	Ile	Ala	Ile	Asn
305					310					315				320	
Gln	Asp	Pro	Leu	Gly	Lys	Gln	Gly	Tyr	Gln	Leu	Arg	Gln	Gly	Asp	Asn
			325					330					335		
Phe	Glu	Val	Trp	Glu	Arg	Pro	Leu	Ser	Gly	Leu	Ala	Trp	Ala	Val	Ala
		340						345					350		
Met	Ile	Asn	Arg	Gln	Glu	Ile	Gly	Gly	Pro	Arg	Ser	Tyr	Thr	Ile	Ala
	355					360					365				
Val	Ala	Ser	Leu	Gly	Lys	Gly	Val	Ala	Cys	Asn	Pro	Ala	Cys	Phe	Ile
	370				375					380					
Thr	Gln	Leu	Leu	Pro	Val	Lys	Arg	Lys	Leu	Gly	Phe	Tyr	Glu	Trp	Thr
385				390						395				400	
Ser	Arg	Leu	Arg	Ser	His	Ile	Asn	Pro	Thr	Gly	Thr	Val	Leu	Leu	Gln
			405						410					415	
Leu	Glu	Asn	Thr	Met	Gln	Met	Ser	Leu	Lys	Asp	Leu	Leu			
			420					425							

What is claimed is:

1. A method of treating Fabry disease, the method comprising administering migalastat to a patient in need thereof, wherein the patient has an α -galactosidase A protein comprising a HEK assay amenable mutation selected from the group consisting of: A13P, A20D, Q57L, G80D, P146S, D175E, K213R, K213M, I242F, M267T, A309V, V316I, V316G, P323R, A352G, R356P, T385A, V390M, and G395A.

2. The method of claim 1, wherein the mutation is selected from the group consisting of: Q57L, G80D, P146S, K213R, K213M, M267T, A309V, V316I, P323R, A352G, R356P, T385A and V390M.

3. The method of claim 1, wherein the mutation is V316I.

4. The method of claim 1, wherein the mutation is selected from the group consisting of: A13P, A20D, Q57L, G80D, P146S, K213R, K213M, I242F, M267T, A309V, V316I, V316G, A352G and R356P.

5. The method of claim 1, wherein the mutation is selected from the group consisting of: A13P, A20D, G80D, P146S, I242F, M267T, V316G and R356P.

6. The method of claim 1, wherein the mutation is selected from the group consisting of: Q57L, G80D, P146S, K213R, K213M, M267T, A309V, V316I, A352G and R356P.

7. The method of claim 1, wherein the mutation is selected from the group consisting of: G80D, P146S, M267T and R356P.

8. The method of claim 1, wherein the mutation is selected from the group consisting of: A13P, A20D, Q57L, G80D,

P146S, D175E, K213M, I242F, M267T, A309V, V316I, V316G, P323R, A352G, R356P, T385A, V390M, and G395A.

9. The method of claim 1, wherein the mutation is selected from the group consisting of: Q57L, G80D, P146S, K213M, M267T, A309V, V316I, P323R, A352G, R356P, T385A and V390M.

10. The method of claim 1, wherein the mutation is selected from the group consisting of: A13P, A20D, Q57L, G80D, P146S, K213M, I242F, M267T, A309V, V316I, V316G, A352G and R356P.

11. The method of claim 1, wherein the mutation is selected from the group consisting of: Q57L, G80D, P146S, K213M, M267T, A309V, V316I, A352G and R356P.

12. The method of claim 1, wherein the patient has a Fabry disease-causing mutation.

13. The method of claim 1, wherein the migalastat or salt thereof is administered to the patient every other day.

14. The method of claim 1, wherein the patient is administered about 123 to about 300 mg of the migalastat or salt thereof every other day.

15. The method of claim 1, wherein the patient is administered about 150 mg of the migalastat or salt thereof every other day.

16. The method of claim 1, wherein the patient is administered about 150 mg of migalastat hydrochloride every other day.

17. The method of claim 1, wherein the patient is male.

18. The method of claim 1, wherein the patient is female.

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19. The method of claim 1, wherein the patient has renal impairment.

20. The method of claim 19, wherein the patient has mild or moderate renal impairment.

21. The method of claim 1, wherein the patient is an enzyme replacement therapy (ERT)-experienced patient.

22. The method of claim 1, wherein the patient is an enzyme replacement therapy (ERT)-experienced patient with renal impairment.

23. The method of claim 1, wherein the patient is an enzyme replacement therapy (ERT)-naïve patient.

24. The method of claim 1, wherein the patient has a proteinuria level of less than 100 mg/24 hr prior to initiating the administration of the migalastat or salt thereof.

25. The method of claim 1, wherein the patient has a proteinuria level of 100 to 1,000 mg/24 hr prior to initiating the administration of the migalastat or salt thereof.

26. The method of claim 1, wherein the patient has a proteinuria level of greater than 1,000 mg/24 hr prior to initiating the administration of the migalastat or salt thereof.

27. The method of claim 1, wherein the migalastat or salt thereof is administered orally.

28. The method of claim 27, wherein the migalastat or salt thereof is in a solid dosage form.

29. The method of claim 28, wherein the solid dosage form comprises a capsule.

30. The method of claim 1, wherein the migalastat is administered as a pharmaceutically acceptable salt.

31. The method of claim 1, wherein the patient is orally administered a capsule comprising about 150 mg of migalastat hydrochloride every other day.

32. The method of claim 7, wherein the patient has a Fabry disease-causing mutation.

33. The method of claim 7, wherein the migalastat or salt thereof is administered to the patient every other day.

34. The method of claim 7, wherein the patient is administered about 123 to about 300 mg of the migalastat or salt thereof every other day.

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35. The method of claim 7, wherein the patient is administered about 150 mg of the migalastat or salt thereof every other day.

36. The method of claim 7, wherein the patient is administered about 150 mg of migalastat hydrochloride every other day.

37. The method of claim 7, wherein the patient is male.

38. The method of claim 7, wherein the patient is female.

39. The method of claim 7, wherein the patient has renal impairment.

40. The method of claim 39, wherein the patient has mild or moderate renal impairment.

41. The method of claim 7, wherein the patient is an enzyme replacement therapy (ERT)-experienced patient.

42. The method of claim 7, wherein the patient is an enzyme replacement therapy (ERT)-experienced patient with renal impairment.

43. The method of claim 7, wherein the patient is an enzyme replacement therapy (ERT)-naïve patient.

44. The method of claim 7, wherein the patient has a proteinuria level of less than 100 mg/24 hr prior to initiating the administration of the migalastat or salt thereof.

45. The method of claim 27, wherein the patient has a proteinuria level of 100 to 1,000 mg/24 hr prior to initiating the administration of the migalastat or salt thereof.

46. The method of claim 7, wherein the patient has a proteinuria level of greater than 1,000 mg/24 hr prior to initiating the administration of the migalastat or salt thereof.

47. The method of claim 7, wherein the migalastat or salt thereof is administered orally.

48. The method of claim 47, wherein the migalastat or salt thereof is in a solid dosage form.

49. The method of claim 48, wherein the solid dosage form comprises a capsule.

50. The method of claim 7, wherein the migalastat is administered as a pharmaceutically acceptable salt.

51. The method of claim 7, wherein the patient is orally administered a capsule comprising about 150 mg of migalastat hydrochloride every other day.

* * * * *

REPLY IN SUPPORT OF AUROBINDO'S MOTION *IN LIMINE* NO. 1

Plaintiffs aim to oppose obviousness by trying to convince the Court that the prior art HEK Assay Aurobindo's references describe was somehow unreliable. *See, generally* Pls' Resp. Exs. A-C. To do this, Plaintiffs rely on their experts, Dr. Hopkin in particular, whose opinions on and around the HEK Assay—including opinions on assay reliability and the effect of assay-related prior art disclosures on POSAs—leave a strong, false impression they are grounded in personal knowledge. *See, e.g.*, Pls' Resp., Ex. B at ¶¶53-58 (describing Plaintiffs' development of different HEK Assays and opining on their reliability); ¶84 (opining on usefulness of HEK Assays to determine amenability); ¶93-104 (discussing patent reference disclosure of HEK Assay); ¶157-165 (differentiating between prior art HEK Assay disclosures and disagreeing with Dr. Medin's opinions regarding significance of disclosures); *see also id.* at ¶¶61-62, 108, 113, 117, 123-126, 141, 142, 148, 150, 178-179, 178-181, 186, 187, 192, 206-207, 211-213, 222-228, 233, 244, 246-248, 251-52, 258-264, 283, 284, 288-291, 295-309, 314, 328-337, 343, 348, 354-358, 363, 381, 408, 409; *see also id.*, Ex. A at ¶51; ¶53; ¶67; ¶81; ¶84; *see also id.*, Ex. C at ¶¶12, 55, 56.

These opinions falsely suggest familiarity with HEK Assay details Plaintiffs' experts clearly and uniformly disclaimed. The explanation for the disparity is simple and hardly controversial, except when, as here, it goes too far and attorneys assisting with report drafting substitute their own opinions for the expert's. *See* Aurobindo Reply Ex. C at 98:11-99:14 (Dr. Hopkin acknowledging being fed attorney opinions); Ex. D at 261:16-22 (Dr. Jeffries describing himself as merely a "strong collaborator" on his reports). Respectfully, neither the Court nor Aurobindo should be forced to waste precious trial time to understand Plaintiffs' experts' lack of qualifications to testify regarding HEK Assays when they have already clearly admitted it under oath. "Smoke and mirrors" is not a valid trial strategy.

EXHIBIT 18

**AUROBINDO'S MOTION *IN LIMINE* NO. 1:
PRECLUSION/EXCLUSION OF PLAINTIFFS'
EXPERT TESTIMONY REGARDING THE HEK ASSAY**

EXHIBIT C



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Transcript of Robert J. Hopkin, M.D.

Date: June 10, 2025

Case: Amicus Therapeutics US, LLC, et al. -v- Teva Pharmaceuticals USA, Inc., et al.

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Transcript of Robert J. Hopkin, M.D.

1 (1 to 4)

Conducted on June 10, 2025

<p>1 IN THE UNITED STATES DISTRICT COURT</p> <p>2 FOR THE DISTRICT OF DELAWARE</p> <p>3 - - -</p> <p>4 AMICUS THERAPEUTICS US, : 5 LLC and AMICUS : THERAPEUTICS, INC., : C.A. No. 1:22-cv-01461-CJB</p> <p>6 Plaintiffs, : ANDA CASE</p> <p>7 vs. : (Consolidated)</p> <p>8 TEVA PHARMACEUTICALS : 9 USA, INC., and TEVA : et al., : 10 Defendants :</p> <p>11 - - -</p> <p>12 VIDEOTAPED DEPOSITION OF ROBERT J. HOPKIN, M.D.</p> <p>13 - - -</p> <p>14 Tuesday, June 10, 2025</p> <p>15 9:04 a.m.</p> <p>16 - - -</p> <p>17</p> <p>18 Held at the offices of:</p> <p>19 Keating Muething & Klekamp, PLL 20 One East Fourth Street, Suite 1400 Cincinnati, Ohio 45202</p> <p>21</p> <p>22 Reported By: Carol A. Kirk, RMR, CSR-9139</p> <p>23</p> <p>24</p> <p>25</p>	<p>1 INDEX TO EXAMINATION</p> <p>2 WITNESS PAGE</p> <p>3 ROBERT J. HOPKIN, M.D.</p> <p>4 CROSS-EXAMINATION BY MR. BARRY 8</p> <p>5</p> <p>6</p> <p>7</p> <p>8</p> <p>9</p> <p>10</p> <p>11</p> <p>12</p> <p>13</p> <p>14</p> <p>15</p> <p>16</p> <p>17</p> <p>18</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p> <p>25</p>
<p>1 A P P E A R A N C E S</p> <p>2 - - -</p> <p>3 On behalf of the Plaintiffs:</p> <p>4 GROOMBRIDGE, WU, BAUGHMAN & STONE, LLP 5 BY: JENNIFER REA DENEALT, ESQUIRE jenna.deneault@groombridgewu.com 6 NAZ E. WEHRLI, ESQUIRE naz.wehrli@groombridgewu.com 7 KYLE N. BERSANI, ESQUIRE kyle.bersani@groombridgewu.com 8 565 Fifth Avenue, Suite 2900 New York, New York 10017 332-269-0030</p> <p>9</p> <p>10 On behalf of the Defendants, Aurobindo Pharma LTD., 11 and Aurobindo Pharma USA, Inc.:</p> <p>12 KRATZ & BARRY, LLP 13 BY: GEORGE J. BARRY, III, ESQUIRE gbarry@kratzandbarry.com 14 1050 Crown Pointe Parkway, Suite 500 Atlanta, Georgia 30338 404-431-6600</p> <p>15</p> <p>16</p> <p>17 ALSO PRESENT:</p> <p>18 Joon Chung</p> <p>19 - - -</p> <p>20</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p> <p>25</p>	<p>1 INDEX TO EXHIBITS</p> <p>2 HOPKIN DESCRIPTION PAGE</p> <p>3 Exhibit 1 Curriculum Vitae of Robert J. Hopkin, M.D. 11</p> <p>4 Exhibit 2 Rebuttal Report of Robert J. Hopkin, M.D. 24</p> <p>5</p> <p>6 Exhibit 3 Document titled "Molecular Genetics and Metabolism Reports" 83</p> <p>7</p> <p>8 Exhibit 4 United States Patent Number 11,633,388 92</p> <p>9</p> <p>10 Exhibit 5 Galafold label 93</p> <p>11 Exhibit 6 Document titled "Sapropterin dihydrochloride, 6-R-L-erythro-5,6,7,8-tetrahydrobiopterin, in the treatment of phenylketonuria" 116</p> <p>12</p> <p>13 Exhibit 7 Document titled "Drugs@FDA: FDA-Approved Drugs" 119</p> <p>14</p> <p>15 Exhibit 8 United States Patent Number 12,042,489 133</p> <p>16</p> <p>17 Exhibit 9 United States Patent Number 12,042,490 133</p> <p>18 Exhibit 10 United States Patent Number 11,833,164 134</p> <p>19 Exhibit 11 United States Patent Number 8,592,362 136</p> <p>20 Exhibit 12 United States Patent Number 2011/0152319, Bates-stamped DEFMIG_0000140 through 312 156</p> <p>21</p> <p>22 Exhibit 13 Document titled "A Pharmacogenetic Approach to Identify Mutant Forms of a-Galactosidase A that Respond to a Pharmacological Chaperone for Fabry Disease" 169</p> <p>23</p> <p>24</p> <p>25</p>

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<p>5</p> <p>1 INDEX TO EXHIBITS (CON'T)</p> <p>2 HOPKIN DESCRIPTION PAGE</p> <p>3 Exhibit 14 Document titled Safety and 172</p> <p>4 pharmacodynamic effects of a</p> <p>5 pharmacological chaperone on</p> <p>6 a-galactosidase A activity and</p> <p>7 globotriaosylceramide clearance</p> <p>8 in Fabry disease: report from</p> <p>9 two phase 2 clinical studies"</p> <p>10 Exhibit 15 Document titled "Amicus 178</p> <p>11 Therapeutics Presents</p> <p>12 Additional 6-Month Results from</p> <p>13 Phase 3 Fabry Monotherapy Study</p> <p>14 at LDN World Symposium"</p> <p>15 Exhibit 16 Document titled "A Phase 2 181</p> <p>16 study of migalastat</p> <p>17 hydrochloride in females with</p> <p>18 Fabry disease: Selection of</p> <p>19 population, safety and</p> <p>20 pharmacodynamic effects"</p> <p>21 Exhibit 17 United States Patent Number 182</p> <p>22 2015/0352093</p> <p>23 Exhibit 18 Document titled "The Validation 191</p> <p>24 of Pharmacogenetics in the</p> <p>25 Identification of Target Fabry</p> <p>Patients for Treatment with</p> <p>Migalastat"</p> <p>Exhibit 19 Deposition of Elfrida Benjamin, 202</p> <p>Ph.D.</p> <p>Exhibit 20 Dr. Elfrida Benjamin Deposition 203</p> <p>Transcript Errata</p> <p>Exhibit 21 Transcript of Jeffrey P. 224</p> <p>Castelli, Ph.D., Designated</p> <p>Representative and</p> <p>Individually, dated February</p> <p>21, 2025</p> <p>Exhibit 22 Dr. Jeffrey Castelli Deposition 224</p> <p>Transcript Errata</p>	<p>7</p> <p>1 Would counsel please voice</p> <p>2 identify themselves and state whom they</p> <p>3 represent.</p> <p>4 MR. BARRY: George Barry, Kratz &</p> <p>5 Barry for Aurobindo.</p> <p>6 MS. DENEALT: Jennifer Deneault,</p> <p>7 Naz Wehrli, Kyle Bersani from</p> <p>8 Groombridge Wu on behalf of Amicus</p> <p>9 Therapeutics, and Joon Chung from Amicus</p> <p>10 Therapeutics.</p> <p>11 THE VIDEOGRAPHER: The court</p> <p>12 reporter today is Carol Kirk</p> <p>13 representing Planet Depos.</p> <p>14 The witness will now be sworn.</p> <p>15 (Witness sworn.)</p> <p>16 MS. DENEALT: And I'd like to</p> <p>17 make a comment at the outset that</p> <p>18 Dr. Hopkin is prepared to address the</p> <p>19 written description and enablement</p> <p>20 references that Dr. Medin makes in the</p> <p>21 context of obviousness in his reply</p> <p>22 expert report.</p> <p>23 MR. BARRY: Thanks.</p> <p>24 - - -</p> <p>25</p>
<p>6</p> <p>1 - - -</p> <p>2 P R O C E E D I N G S</p> <p>3 - - -</p> <p>4 THE VIDEOGRAPHER: Here begins</p> <p>5 media number 1 in the videotaped</p> <p>6 deposition of Robert J. Hopkin M.D., in</p> <p>7 the matter of Amicus Therapeutics US,</p> <p>8 LLC, et al. v. Teva Pharmaceuticals USA</p> <p>9 Inc. et al. in the United States</p> <p>10 District Court for the District of</p> <p>11 Delaware, Case Number 1:22-cv-01461-CJB.</p> <p>12 Today's date is June 10, 2025.</p> <p>13 The time on the video monitor is</p> <p>14 9:04 a.m. Eastern Standard Time.</p> <p>15 The remote videographer -- I'm</p> <p>16 sorry. The regular videographer today</p> <p>17 is Michael Harden representing Planet</p> <p>18 Depos.</p> <p>19 All parties of this video</p> <p>20 deposition are attending at the law</p> <p>21 offices -- sorry. I lost my place.</p> <p>22 Stand by.</p> <p>23 All parties are attending at the</p> <p>24 law offices of Keating Muething &</p> <p>25 Klecamp PLL.</p>	<p>8</p> <p>1 ROBERT J. HOPKIN, M.D.</p> <p>2 being by me first duly sworn, as hereinafter</p> <p>3 certified, deposes and says as follows:</p> <p>4 CROSS-EXAMINATION</p> <p>5 BY MR. BARRY:</p> <p>6 Q. Good morning, Dr. Hopkin.</p> <p>7 A. Good morning.</p> <p>8 Q. We met briefly. I'm George Barry.</p> <p>9 I represent Aurobindo in this case.</p> <p>10 Thank you for being with us here</p> <p>11 today.</p> <p>12 Before we get started, have you ever</p> <p>13 been deposed before?</p> <p>14 A. Yes, I have.</p> <p>15 Q. About how many times?</p> <p>16 A. I don't remember.</p> <p>17 Q. Is it more than ten?</p> <p>18 A. No. Probably less than ten.</p> <p>19 Q. When was the last time you were</p> <p>20 deposed?</p> <p>21 A. I don't remember that either.</p> <p>22 Q. Was it in the last five years?</p> <p>23 A. Yes.</p> <p>24 Q. Okay. Do you remember what -- what</p> <p>25 you have in mind? What the nature of your</p>

Conducted on June 10, 2025

<p>97</p> <p>1 Q. Well, look down at the very last 2 sentence there. It says -- I'll read that one 3 into the record. "Mutations that have previously 4 been identified as responsive to a PC (e.g. 5 migalastat) using these methods are listed in 6 U.S. Patent Number 8,592,362, which is hereby 7 incorporated by reference in its entirety." 8 Did I read that correctly? 9 A. Yes. 10 Q. Are you familiar with the '362 11 patent referred to in here? 12 A. I would have to look at it. 13 Q. We'll have to come back to it. 14 [REDACTED] 15 [REDACTED] 16 [REDACTED] 17 [REDACTED] 18 [REDACTED] 19 Q. So the words "previous screening 20 methods" doesn't make you think that maybe they're 21 talking about earlier assays? 22 A. I would have to read a couple pages 23 and try to figure context. To assess the previous 24 screening could be used in a number of different 25 ways.</p>	<p>99</p> <p>1 actually -- what reflects your own independent 2 opinions and what might be provided. And we all 3 do this very similarly. So there's obviously 4 going to be stuff that we've -- that the attorneys 5 provided to Dr. Medin because he's not a patent 6 attorney. 7 So did the definition of POSA, 8 person of ordinary skill in the art, in paragraph 9 29 -- is that something that you independently 10 came up with, or is that something that was 11 provided to you? 12 A. Honestly, that was a definition that 13 came out of a combination of things that were 14 provided to me in discussion with counsel. 15 Q. So you were -- you did have input 16 into this definition of POSA; is that correct? 17 A. Yes. 18 Q. How did you go about evaluating a 19 person of ordinary skill in the art? 20 A. The person of ordinary skill in the 21 art was described to me. They showed me 22 definitions, explained what the concept was. 23 I commented that I think it's a little bit 24 ambiguous and difficult to use. 25 But in thinking about the field in</p>
<p>98</p> <p>1 Q. All right. So looking back at your 2 report again. Now I'm looking back at paragraphs 3 28 through 33. You talk about a person of 4 ordinary skill in the art, correct? 5 A. Yes. 6 Q. I first note in the paragraph 28, 7 you've identified priority dates, May 30, 2017 and 8 August 7, 2019. 9 Did you come up with those dates? 10 A. No. 11 Q. Did you do an independent evaluation 12 to determine whether those are, in fact, the 13 correct priority dates? 14 A. I read the materials that were 15 provided to me, and those were the listed dates. 16 Q. Did you independently evaluate -- 17 you know, do a priority date evaluation yourself 18 to determine what the priority dates were, or is 19 that information you received from counsel? 20 A. I did not do an independent looking 21 into the dates. 22 Q. I mean, some of this is just trying 23 to understand what you might be talking about at 24 trial. So I'm not trying to trick you here. I'm 25 just trying to understand whether you've</p>	<p>100</p> <p>1 which the question is placed, what would somebody 2 need to be considered a POSA based on the 3 definitions that were provided to me of how that 4 concept works. 5 Q. So one of the criteria that you 6 evaluated was the field of the -- the field of 7 study or the field of art; is that right? 8 A. Right. 9 Q. And what were the other criteria 10 that you evaluated? 11 A. Years of experience. 12 Q. Whose experience were you 13 evaluating, I guess? 14 A. What's a POSA. That's the person. 15 That's whose experience. How much experience does 16 it take to be a person, a POSA. 17 Q. All right. And then what was 18 another one? 19 A. I honestly don't remember all of the 20 things that were considered or discussed. 21 Q. Why didn't you put it in the details 22 of your evaluation in your report? 23 A. I'm trying to think of a way to 24 explain the process. And there's a lot of things 25 that go through my head, and I can't list all of</p>

EXHIBIT 18

**AUROBINDO'S MOTION *IN LIMINE* NO. 1:
PRECLUSION/EXCLUSION OF PLAINTIFFS'
EXPERT TESTIMONY REGARDING THE HEK ASSAY**

EXHIBIT D



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Transcript of John L. Jefferies, M.D.

Date: June 26, 2025

Case: Amicus Therapeutics US, LLC, et al. -v- Aurobindo Pharma, Ltd., et al.

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Transcript of John L. Jefferies, M.D.
Conducted on June 26, 2025

1 (1 to 4)

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25	1 UNITED STATES DISTRICT COURT THE DISTRICT OF DELAWARE -----X AMICUS THERAPEUTICS US, LLC and AMICUS THERAPEUTICS, INC., Plaintiffs, v. C.A. No. AUROBINDO PHARMA LTD., AND 1:22-cv-01461-CFC AUROBINDO PHARMA USA, INC., Defendants. -----X DEPOSITION OF JOHN L. JEFFERIES June 26, 2025 Reported by: MARY F. BOWMAN, RPR, CRR JOB NO. 589348	3 APPEARANCES: GROOMBRIDGE, WU, BAUGHMAN & STONE LLP Attorneys for Plaintiffs 565 Fifth Avenue, Suite 2900 New York, New York 10017 BY: JENNIFER REA DENAULT, ESQ. HAYLEY LEBLANC, ESQ. CARISSMA MCGEE, ESQ. KRATZ & BARRY, LLP Attorneys for Defendants 1050 Crown Pointe Parkway, Suite 500 Atlanta, Georgia 30338 BY: GEORGE J. BARRY III, ESQ. Also Present: Joon Chung, Amicus Therapeutics Robert Palos, Legal Videographer
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25	2 June 26, 2025 9:00 a.m. Deposition of JOHN L. JEFFERIES, held at Groombridge, Wu, Baughman & Stone LLP, 565 Fifth Avenue Suite 2900 New York, New York, before Mary F. Bowman, a Registered Professional Reporter, Certified Realtime Reporter, and Notary Public of the States of New Jersey and New York.	4 THE VIDEOGRAPHER: Here begins media number 1 in the videotaped deposition of John L. Jefferies, M.D., in the matter of Amicus Therapeutics US, LLC, et al., versus Aurobindo Pharma LTD, et al., in the United States District Court for the District of Delaware, Case Number 1:22-cv-01461-CFC, and 1:22-cv-01461-CJB. Today's date is June 26, 2025. The time on the monitor is 9:01 a.m. The videographer today is Robert Palos representing Planet Depos. The video deposition is taking place at 565 Fifth Avenue, New York, New York. Would counsel please voice-identify themselves and state whom they represent. (Whereupon, counsel placed their appearances on the audio record.) THE VIDEOGRAPHER: The court reporter today is Mary Bowman representing Planet Depos. The witness will now be sworn in. - - -

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<p>5</p> <p>1 JOHN L. JEFFERIES, 2 called as a witness by the defendants, 3 having been duly sworn, testified as 4 follows: 5 EXAMINATION BY 6 MR. BARRY: 7 Q. Good morning, Dr. Jefferies. 8 A. Good morning, sir. 9 Q. I briefly introduced myself earlier. 10 I'm George Barry. I represent Aurobindo. Thank 11 you for being with us here today. 12 I'm just going to get started with 13 some questions. 14 When did the need for a migalastat 15 treatment for Fabry patients with the Y184S 16 mutation begin in your opinion? 17 A. Well, I would -- that's in my 18 statements that I submitted for review. If 19 possible, we could through those together. 20 Q. Do you recall offering an opinion 21 specifically about when a need for migalastat 22 treatment for the Y184S mutation began in your 23 opinions? 24 A. As I said, it's in my statement. I 25 would be happy to review those with you, sir.</p>	<p>7</p> <p>1 being or would it be -- would the need for 2 migalastat arise later? 3 A. In my opinion, the need for 4 migalastat would be based on if the mutation 5 that we're referencing, which could be agnostic, 6 was felt to be amenable to the therapy with 7 migalastat. 8 Q. So if I understand your testimony, 9 it is your opinion that the need for migalastat 10 therapy for a particular mutation would not 11 arise until that mutation was identified as 12 amenable for treatment with migalastat, is that 13 correct? 14 A. Well -- 15 MS. DENEULT: Objection to form. 16 A. I'm sorry. 17 Q. You can answer the question. 18 A. No, that's fine. 19 Q. No, you have to answer the question. 20 Sorry. Unless she tells you not to answer the 21 question, you have to answer the question. 22 A. Okay. 23 I think the unmet need was there 24 prior to any recognition of the mutation per se 25 as far as particular opportunities in patients.</p>
<p>6</p> <p>1 Q. So you believe that in your 2 statement, in your opinions, that you have 3 actually offered an opinion as to when the need 4 for migalastat treatment for the Y184S mutation 5 began? 6 A. I offered an opinion about an unmet 7 need specific to mutations that were approved in 8 the migalastat initial submission, yes, sir. I 9 offered an opinion about the unmet need. 10 Q. And what I'm asking about is when 11 the need arose, not necessarily when the unmet 12 need was recognized. 13 So for any of the mutations that are 14 in the asserted claims, what in your opinion 15 would be -- when did the need for a migalastat 16 treatment for those mutations arise in your 17 opinion? 18 A. Once again, I mean, we can refer to 19 my submissions and go through those line by line 20 if you would like, sir. 21 Perhaps I'm not completely 22 understanding what you're asking me. 23 Q. Well, would the need for migalastat 24 for a particular mutation, would it arise when 25 the mutation first presented itself in a human</p>	<p>8</p> <p>1 But for migalastat particularly, the indications 2 are for approved mutations that are amenable to 3 migalastat therapy. 4 Q. So if I try to break that down a 5 little bit, if I understand correctly, you're 6 saying there is a need for treatment before the 7 mutation is identified as amenable, is that 8 fair? 9 A. No. What I am saying, there is the 10 need for treatment, and I need to define what 11 the best treatment strategy is. And by 12 understanding the mutation status has helped me 13 define what the treatment strategy is to be 14 pursued. 15 Q. So would a mutation that was 16 amenable to migalastat though, would the need 17 for migalastat arise before the mutation was 18 actually identified as amenable? 19 A. I'm sorry, maybe I'm not 20 understanding your logic there. So please 21 rephrase or ask that again. I apologize. 22 Q. Sure. 23 So would the need for migalastat for 24 a mutation that we now know is amenable, would 25 the need for migalastat have arisen for that</p>

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<p style="text-align: right;">261</p> <p>1 explaining it now.</p> <p>2 Q. And, in fact, you can testify</p> <p>3 honestly and truthfully that nowhere in your</p> <p>4 report do you point to an example of a person of</p> <p>5 ordinary skill in the art identifying the</p> <p>6 engineered mutations at all prior to</p> <p>7 August 2019, correct?</p> <p>8 A. That's my recollection, sir, in the</p> <p>9 report.</p> <p>10 Q. All right. Let's talk about</p> <p>11 Exhibit 10 again, where the date is in doubt --</p> <p>12 A. I apologize, just one second.</p> <p>13 Yes, sir.</p> <p>14 Q. You got Exhibit 10?</p> <p>15 A. Yes, sir.</p> <p>16 Q. I didn't write your expert reports,</p> <p>17 did I?</p> <p>18 A. No, sir.</p> <p>19 Q. Oh.</p> <p>20 Did you write your expert reports?</p> <p>21 A. I was a strong collaborator, yes. I</p> <p>22 wrote them in conjunction with the legal team.</p> <p>23 Q. And when we started out today, I had</p> <p>24 asked you if you reviewed the reports, correct?</p> <p>25 A. Yes, sir. Yes, sir.</p>	<p style="text-align: right;">263</p> <p>1 A. Yes, sir.</p> <p>2 THE VIDEOGRAPHER: No further</p> <p>3 questions?</p> <p>4 MS. DENEALT: Wait, can I do a</p> <p>5 two-minute break?</p> <p>6 THE VIDEOGRAPHER: We are going off</p> <p>7 the record. The time on the monitor is</p> <p>8 4:37 p.m.</p> <p>9 (Recess.)</p> <p>10 THE VIDEOGRAPHER: We are back on</p> <p>11 the record at 4:40 p.m.</p> <p>12 MS. DENEALT: Dr. Jefferies, no</p> <p>13 further questions. Thank you.</p> <p>14 THE WITNESS: Thank you.</p> <p>15 MR. BARRY: Thanks again,</p> <p>16 Dr. Jefferies.</p> <p>17 THE WITNESS: Thank you, sir.</p> <p>18 (Continued on next page for jurat.)</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p> <p>25</p>
<p style="text-align: right;">262</p> <p>1 Q. And I had asked you if there was</p> <p>2 anything you wanted to correct, right?</p> <p>3 A. Um-hm. Yes, sir.</p> <p>4 Q. Was that reference -- did your</p> <p>5 citation to Exhibit 10, did you get the date</p> <p>6 wrong on that when you described it as being</p> <p>7 published in February of 2016?</p> <p>8 A. I may have. I'd have to review my</p> <p>9 document, but at the time you asked me, that</p> <p>10 wasn't something that I was thinking about.</p> <p>11 Q. Or was that something that your</p> <p>12 attorneys messed up for you?</p> <p>13 A. No, I reviewed the document and gave</p> <p>14 final approval. So if there was some problem</p> <p>15 there, I'll absorb that concern.</p> <p>16 Q. So do you want to change that</p> <p>17 citation now, do you think, or might there be a</p> <p>18 reason that you have for believing that that</p> <p>19 document was actually prepared in 2016?</p> <p>20 A. I would probably want to talk with</p> <p>21 the legal team before I made any changes to my</p> <p>22 documents, sir.</p> <p>23 Q. Fair enough.</p> <p>24 I got nothing else. Thank you,</p> <p>25 Doctor.</p>	<p style="text-align: right;">264</p> <p>1 THE VIDEOGRAPHER: This concludes</p> <p>2 the deposition of John L. Jefferies, M.D.</p> <p>3 We are going off the record at 4:40 p.m.</p> <p>4</p> <p>5 _____</p> <p>6 JOHN L. JEFFERIES</p> <p>7</p> <p>8 Subscribed and sworn to</p> <p>9 before me this day</p> <p>10 of MO , 2024.</p> <p>11</p> <p>12 _____</p> <p>13</p> <p>14</p> <p>15</p> <p>16</p> <p>17</p> <p>18</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p> <p>25</p>